

## THE DYSENTERIC DISORDERS

# THE Dysenteric Disorders

*The Diagnosis and Treatment  
of Dysentery, Sprue, Colitis and other Diarrhæas  
in General Practice*

By

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2nd Edition  
—

WITH AN APPENDIX

by

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*Technical Assistant*

*With 9 Colour and 14 Black and White  
Plates and 108 Illustrations in the Text*



CASELL AND COMPANY, LTD.

LONDON, TORONTO BOMBAY, MELBOURNE AND SYDNEY

1943

FIRST PUBLISHED . . . 1939  
SECOND EDITION . . . 1943

**DEDICATED**

**TO**

**My Medical Colleagues and the Nursing Staff  
of the Hospital for Tropical Diseases,  
London**



## PREFACE TO THE FIRST EDITION

Behold O Lord for I am in distress my bowels are troubled  
*Lamentations, 1, 20*

My liver is poured upon the earth  
*Lamentations, 11 11*

DURING the last thirty years it has become more generally recognized that many forms of disease of the bowels exist and are caused by entirely different agents although the outward signs and symptoms may closely resemble one another.

Many of the organisms responsible have now been classified and studied extensively their life histories have been worked out and therapeutic agents which act directly upon them discovered. The present is therefore an opportune occasion to digest and review the existing knowledge on the dysenteric diseases and to assess in some measure the value of the different forms of treatment which have been elaborated.

It is felt that there is a real need for a comprehensive account of the dysenteries the various forms of colitis sprue helminthic diseases and the different diarrheas which form such a complex assembly in general and consulting practice. In addition to dysenteries there are many affections of the colon—the various and enigmatical forms of colitis by no means peculiar to warm countries—which bulk largely in practice and upon which a great deal of more accurate information is much to be desired.

It is with the aim of stimulating research upon these unsolved problems and with the idea of utilizing the comparative method of study—comparing the known with the unknown—that this work has been taken in hand. Much of the information which is made available in this book exists already widely scattered throughout the literature.

The differential diagnosis of the various forms of colitis from the better known forms of dysentery is one which confronts the practitioner in the tropics almost daily but it is necessary to state that this book, although it embraces a number of conditions which are generally regarded as tropical has not been undertaken solely from that specialized viewpoint rather has it been written from the standpoint of general medicine. In hardly any

other branch of the medical art are the niceties of differential diagnosis so important. It is, for instance, a gross error to diagnose and treat acute bacillary dysentery, or acute colitis, as intestinal amœbiasis, and therefore to inject large doses of emetine—a particularly toxic drug.

Having been engaged more or less continuously for over thirty years in the study of this subject from the bacteriological, pathological and clinical aspects, I have drawn largely from my own records; indeed I have endeavoured to make this book the outcome of a life's study. As an example, the numbers of cases studied at the Hospital for Tropical Diseases in the preparation of the clinical section of this work are as follows:—

Chronic bacillary dysentery .. ..	107	
Amœbic dysentery (definitely diagnosed)	535	
Sprue .. ..	423	(males 265,
Ulcerative colitis .. ..	42	females 158)
Polypus .. ..	14	
Polyposis .. ..	4	
Mucous colitis .. ..	116	
Intestinal tuberculosis .. ..	13	
Intestinal bilharziasis .. ..	15	
Gall-bladder diseases .. ..	30	
Duodenal ulcer .. ..	40	
Appendicitis .. ..	73	
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The more technical aspects, the zoological description of the intestinal protozoa and bacteria, the methods employed in their cultivation and recognition, and various other details are gathered together in the form of an appendix, in the compilation of which I have received the loyal co-operation of my friend and Technical Assistant, Mr. W. J. Muggleton, with whom I have been closely associated for the past twenty-eight years.

My best thanks are also due to Drs. W. E. Cooke, F.R.C.S.I., and J. N. Strauss, M.B.C.P., for many kindly suggestions in the preparation of this work.

PHILIP MANSON-BAHR.

149, Harley Street,  
London, W.1.  
January, 1939.

## PREFACE TO THE SECOND EDITION

SINCE the publication of this work three years ago serious and vital events have taken place which have disturbed and too often barbarously checked the ordered progress of scientific thought and work. Though the horrors of mechanised warfare have changed the tenets and habits of men they have in no way altered the inherent nature of pathogenic organisms and the ravages of disease. These remain as ever, inevitable accompaniments of war and a menace to mankind so that it is only reasonable to expect that dysenteric conditions will play as great a part in the outcome of this world conflict as they did in the similar catastrophe a quarter of a century ago.

As I have been actively engaged in the investigation and treatment of the dysenteries since 1909 it fell to my lot to benefit by an unexampled experience of these diseases in the Middle East during the whole period of the last war. The results of these laboratory investigations and their clinical application in times of war and peace set forth in these pages were prefaced by special researches undertaken on dysentery and sprue in Fiji and Ceylon during the years 1909-1918.

Though no vital alterations have been made in the general arrangement of the book mention is made of the many improvements effected in treatment especially the introduction of sulphaguanidine in bacillary dysentery. In view of the recent new light on the aetiology of the sprue syndrome and the relationship of this interesting symptom complex to the steatorrhoëas and fat absorption a new chapter on pellagra has been inserted, a better understanding of the complexities of this nutritional disorder having shed much light upon the group of diseases with which it has many aspects in common.

The demand for this second edition has been evoked by the present cataclysm as well as by the necessity of including many advances in aetiology, diagnosis and treatment which in the interval have become available. It is hoped that, by their timely publication in an easily assimilable form the volume may become helpful to all in the armed forces or medical services at home or abroad who may be called upon to treat the many varied and puzzling phases of the dysenteric disorders. With this end in view I have tried by every means in my power to make this revision as complete as possible. In so doing I have been encouraged by the generous reception afforded by the profession to the first edition of the work.

PHILIP MANSON BARR

149 Harley Street W 1

February 1942

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## INTRODUCTION

By J. JOHNSTON ABRAHAM, CBE, DSO, FRCS

Author of "*The Surgeon's Log*," etc

THIS is a book that needed to be written, and the wonder is that such a work had not been attempted before. Probably the reason is that it required an experience both of European and tropical diseases of the alimentary tract such as few possess, coupled with an industry in collecting and tabulating what has been written on the subject in scattered papers in several languages that would daunt all but the most intrepid. Dr. Manson-Bahr possesses both the experience and the courage to tackle this task. He has done so in the book before us, and the profession accordingly owes him a debt of gratitude.

The history of the differentiation of the dysenteries is an important one. The dysentery amoeba was discovered by Loesch in 1875, and the dysentery bacillus by Shiga in 1898. This time-lag has been unfortunate, since it has produced a general belief in the minds of many that all dysenteries in the tropics must be amoebic, while it is still not fully recognized that bacillary dysentery is of the two the more widespread and important.

This was especially so in the Great War. It was bacillary dysentery and not the Turk that drove us out of Gallipoli. With proper precautions we should never have had an epidemic of dysentery there, for the disease is a fly-borne one, as Manson-Bahr proved in Fiji in 1911. To make things worse, the outbreak in Gallipoli was treated as amoebic dysentery, with disastrous results, many lives being lost through this diagnostic blunder. It is a distressing thought upon which one does not care to dwell.

Luckily, by the time the remnants of the troops came back to Egypt, the mistake had been discovered, and throughout the Sinai campaign the elaborate precautions taken to prevent fly-breeding protected the great base camps from any further outbreak. This was a very remarkable feat when one considers that at Kantara on the Suez Canal there were one hundred and twenty thousand men with no sanitation except field latrines, and that British, Colonial, Indian and European troops were all camping



alongside one another. None the less, the military mind still clung to the idea that amœbic dysentery would be found endemic in Indian troops, and all sorts of absurd regulations were made about hospital trains and every difficulty put in the way of transporting troops through Italy to the Western front.

A knowledge of the dysenteries is of increasingly great diagnostic importance to all practitioners of medicine both at home and in the tropics. For as the time distance between countries decreases and people travel more and more the risk of infection mathematically increases and we may expect to see more and more diseases once confined to the tropics, in every day practice in Europe.

There is however no likelihood of amœbic dysentery ever becoming endemic in the British Isles owing to the excellence of our sanitary arrangements but a knowledge of the dysenteries is essential if one is to understand the extent and treatment of colitis, enteritis and other similar abdominal diseases, and the wonders that can be done by the proper utilization of the modern drugs now at our disposal should be familiar to all.

Dr. Manson Bahir's treatise is a mine of information on these subjects.

# DYSENTERIC DISORDERS

## CHAPTER I

### METHOD OF PROCEDURE IN INVESTIGATING A CASE OF DIARRHŒA OR DYSENTERY

IN the complete investigation of the causes of acute and chronic diarrhœa and the many diverse conditions which border upon dysenteric disorders, it is necessary to bring into play most of the resources at the disposal of the modern physician, elucidation of a case, therefore, requires an extensive knowledge of medicine in general.

In Table I will be found a list of the known causes of diarrhœa in adults and children, but to describe all these *in extenso* would entail the compilation of a complete medical textbook. This is far from being the object of the table, which is designed as a means of conveying to practitioner and student the wide range of the subject, and of suggesting details to which his special attention should be directed. In Table II are classified the different steps, in due order, which should be undertaken in the investigation of a patient suffering from diarrhœa or dysentery.

The special diseases with which this book deals are those which in some form or other, fall into the dysenteric syndrome, and these demand special laboratory methods to establish a diagnosis. The main interest of the book centres round the subject of the dysenteries and colitis, and within it diagnosis and treatment are handled at some length with the idea of assisting the specialist, practitioner and student to obtain an insight into an admittedly complex subject.

TABLE I

#### CLASSIFICATION OF THE CAUSES OF DIARRHŒA

##### IN ADULTS

##### *Primary diarrhœa*

Diet

Constipation

Changes of climate, or weather

Irritants taken with food—mushrooms, mercury, arsenic or ptomaine poisoning

##### *Alterations of intestinal secretion or absorption*

Acute and chronic dyspepsia (gastrogenous), pancreatogenous diarrhœa, cholecystitis

Idiopathic steatorrhœa (celiac disease), non tropical and tropical sprue, hill diarrhœa

Nervous diarrhœa

*Secondary diarrhœa* Infective conditionsTyphoid and paratyphoid fevers (*Salmonella* group)

Bacillary dysentery—Shiga, Schmitz, Flexner and Sonne infections

Cholera

Gertner and Aertrycke infections

Amoebiasis and amoebic dysentery, balantidiasis, giardiasis, flagellate diarrhœa, coccidiosis, malarial dysentery, leishmanial dysentery

Trichinosis, bilharziasis, fasciolopsis, heterophyes and other worm infections

*General infections*

Endocarditis, septicæmia and pulmonary tuberculosis

*Diseases of intestines*

Carcinoma

Tuberculosis

Syphilis

Actinomycosis

Diverticulitis

Chronic cicatrizing enteritis (Crohn's disease)

Peritonitis

Appendicitis

Hæmorrhoids

*Blood diseases*

Henoch's and other forms of purpura

*Chronic circulatory disturbance*

Portal congestion

Cirrhosis of the liver

Chronic heart and lung disease

*Toxic*

Hyperthyroidism (thyrotoxicosis)

Chronic alcoholism

Uræmia

Lardaceous disease

*Avitaminosis*

Pellagra and prepellagrous conditions

*Special types of diarrhœa*

Ulcerative colitis

Mucous membranous colitis

Polypoid

Polypus

Stereocal ulceration

Foreign body in rectum

## IN CHILDREN

Diarrhœa and vomiting (summer diarrhœa)

Simple diarrhœa from chills and errors in diet

Acute gastro enteritis, summer diarrhœa, bacillary dysentery—Shiga,

Flexner, or Sonne infection

Amoebic dysentery

Celiac disease

Intussusception

Polypus

TABLE II

## METHOD OF PROCEDURE IN THE INVESTIGATION OF A PATIENT SUFFERING FROM DIARRHŒA\*

## 1. History.

Features in history indicating possible causes

Sharpness of onset or chronicity

Dietetic habits

Previous residence in the tropics noting particularly geographical distribution of intestinal disease

Liability to chills

## 2. General Examination —Paying special attention to —

(a) *Skin* Petechiæ (septic endocarditis)

Texture (endocrine disease)

Pigmentation (kala azar, Addison's disease, arsenic, etc.)

(b) *Neck* Thyroid (hyper or hypothyroidism)(c) *Lungs* Tuberculosis, compression signs as in amoebic abscess of liver, pulmonary abscess(d) *Cardio vascular* Congestion septic endocarditis(e) *Tongue* Sprue, pellagra, idiopathic steatorrhœa, syphilis, gastroenterous diarrhœa(f) *Central Nervous System* Lesions causing incontinence—e.g. tabes, etc(g) *Glands* Inguinal bubo if suggestive Frei-Hoffmann test in lymphogranuloma, leukaemia(h) *Abdomen* Palpation

Masses—carcinoma of colon, diverticulitis, bilharziasis, amoebiasis, tuberculoma, actinomycosis, intussusception

Doughy (tuberculosis)—sprue or steatorrhœa

Enlarged spleen or liver—cirrhosis, carcinoma, malaria, leukaemia, etc

## 3. Digital rectal examination

Carcinoma, piles, stricture, velvety feel of ulcerative colitis, chronic rectal amoebic ulcer, stricture of lymphogranuloma

Fæcal impaction

## 4. Stool examination — (3 stools should be examined if possible)

(a) *Naked-eye appearance*—Dysenteries, sprue (If suggestive—then fat analysis, occult blood, test meal, glucose curves)(b) *Helminth eggs* Bilharzia, ancylostoma, fasciolopsis, heterophyes, etc(c) *Protozoa* Amœbæ, balantidium, giardia, coccidium, etc(d) *Charcot-Leyden crystals*

## 5. Blood examination.

Count—sprue, anæmia

Parasites—malaria

Serum agglutination—against dysenteries and the Salmonella group

Leucocyte count and differential count of value in amoebiasis and tuberculosis Eosinophilia in trichinosis bilharziasis, etc

\*This is to be considered as a mere outline containing points which a practitioner should bear in mind on approaching a case

6. **Urine.**—Casts etc.—uræmia (If suggestive blood uræa) Porphyrinuria in pellagra and sprue
7. **Wassermann.**—Tabes Rectal stricture
8. **Sigmoidoscopy.**—Numerous lesions diagnosed thereby—dysenteries, carcinoma polypus and polyposis, ulcerative colitis, etc
9. **Barium enema**—Growths, colitis of different kinds
- 10 **Barium meal**—Appendicitis, diverticulitis stenosis stricture, tumour, regional ileitis (Crohn's disease)

There are dysenteriform diseases in which the clinical picture is so striking that they may almost be diagnosed at sight, there are others in which prolonged laboratory investigations must be undertaken before an exact diagnosis is possible

In many instances, from the actual physical examination and appearances of the patient no positive information can be elicited This is often the case in amebiasis and in the milder forms of bacillary dysentery Special attention must be paid to the presence or absence of wasting and to the general appearance of the abdomen, whether sunken navicular, swollen or turgid

Other important points in the examination of the abdomen are the presence or absence of meteorism, areas of tenderness discovered on deep pressure, a sensation of spasticity of the colon, or actual thickening of its walls The size and consistency of the liver discovered by deep percussion or palpation are important, as is also discomfort directed towards the gall bladder The colouring and general features of the complexion and texture of the skin must also be noted

After the physical examination of the patient comes the positive information derived by proctoscopy or sigmoidoscopy, by which means a view of the mucous membrane may be obtained At the same time the all important microscopical examination of the fæces must be undertaken—an extensive and specialized subject—the presence or absence of inflammatory cells and blood and the character of the non digested contents being duly noted The search for intestinal protozoa or the eggs of helminths should be carried out with a comparatively low power lens (i.e.  $\times 10$ ) before proceeding to the more elaborate bacteriological culture of the stools

Finally, with a due sense of proportion as to the value of information thus obtained, the radiosopic examination of the bowel should be conducted Probably much more accurate knowledge is vouchsafed by a barium enema, in studying the outline of the colon movements and texture than from a barium meal, and here the newer methods of air inflation with measured doses constitute a more valuable aid than the older measures of mass infiltration

Biochemical methods may have to be invoked The fractional test meal, van den Bergh reaction of the serum, and the sugar tolerance tests have each their appropriate place

Thus in the full elucidation of a case of dysenteric disease, or of chronic diarrhœa, nearly all the ancillaries of medical practice may be called upon in their appropriate sphere. Many of these methods are not readily available to the general physician, and therefore every effort is made in this book to guide him in the simpler means of investigation which actually still remain of most value, and which are always at his command.

## CHAPTER II

### THE EXAMINATION OF THE BOWEL WITH SPECIAL REFERENCE TO SIGMOIDOSCOPY

With the great majority of patients it becomes necessary to undertake a local examination of the bowel. This is especially the case when complaint is made of symptoms referable to the rectal canal, and even in cases of genuine dysentery. It should always be done unless the diagnosis has been rendered absolutely certain by the recognition of the causative parasite in the stools. It cannot too strongly be emphasized that grave mistakes are bound to occur unless a local inspection of the bowel itself is made, and it is obvious that by no other means can malignant growths in their early stage be recognized and dealt with adequately. The patient may seek advice solely on account of piles, but the external appearance of hemorrhoids may be only a warning sign of a more severe pathological lesion higher up the intestinal tract.

There are several methods of examining the bowel. For the diagnosis of hemorrhoids, anal fissures, and fistulæ the local examination of the rectum with a suitable proctoscope is sufficient, but for any more extensive investigation a sigmoidoscope is necessary. Digital examination of the rectum should never be neglected. This is most important from the viewpoint of the practitioner.\*

#### IMPORTANT POINTS IN THE SURGICAL ANATOMY OF THE ANUS AND RECTAL CANAL

E. T. C. Milligan and C. N. Morgan in their study of the surgical anatomy of the anal canal, have laid stress on the fact that the various musculatures of the bowel can and should be palpated and recognized. The external sphincter of the anus is a trilaminar muscle which with the puborectalis portion of the levator ani forms a strong muscular cylinder encircling the longitudinal muscle, the internal sphincter ani and the anal canal. The three layers are named, from below upwards, 1, the sphincter ani externus subcutaneus, 2 the sphincter ani externus superficialis, 3 the sphincter ani externus profundus. The first and third portions are annular muscles not attached to the coccyx, the second portion is elliptical and is attached to the coccyx. The second and third parts encircle the longitudinal muscle and the internal sphincter ani.

The levator ani muscle itself may also be divided into three portions —

1 The *iliococcygeus*, arising from the ischial spine and from the posterior part of the white line. It is inserted into the coccyx<sup>1</sup> and the ano coccygeal raphé. It is usually only represented by fibrous tissue and may be regarded as a degenerating muscle whose primary function—flexion of the tail—has been lost.

2 The *pubococcygeus*, which arises from the back of the os pubis and from the anterior part of the obturator fascia, the fibres are directed backwards horizontally along the rectum at a higher level than the puborectalis.

3 The *puborectalis* arises from the back of the symphysis pubis and forms the upper part of the triangular ligament. From this origin the fibres pass backwards and also downwards around the lower and lateral aspect of the rectum, meeting with fibres from the opposite side behind the anal canal, so forming a powerful loop which slings the ano rectal junction to the symphysis.

The *longitudinal muscle* of the anal canal is a prolongation of the external muscular coat of the rectum surrounding the anal canal. At the upper end of this canal it at once becomes fibromuscular, blending in its posterior half with the puborectalis and in its anterior half with the external sphincter ani profundus, and there takes its shape in the formation of the *ano rectal ring*.

The *sphincter ani externus subcutaneus* is easily palpated and recognized in its whole extent as a round or elliptical band situated at the verge of the anus immediately under the skin. It is about one quarter of an inch in thickness, and at its upper and inner edge there is encircling the canal, a well marked depression, one quarter to an eighth of an inch wide, called the *anal intermuscular septum*. This separates the muscle from the more easily recognized lower and rounded edge of the internal sphincter which itself reaches to within a quarter of an inch of the anal margin. The *sphincter ani externus subcutaneus* is the only portion of the external sphincter which is subcutaneous and is directly palpable throughout. The lower border of the internal sphincter can be palpated as the rounded upper boundary of the intermuscular septum encircling the anal canal. It extends below the muco cutaneous junction to within a quarter of an inch of the anal margin.

The *ano rectal ring* is situated at the junction of the anal canal and rectum. It is found to be a composite fibromuscular band composed of the upper portion of (a) the internal sphincter, (b) the longitudinal muscle, (c) the puborectalis, and (d) the external sphincter ani profundus muscles. It should be possible, by withdrawing and inserting the palpating finger with pressure at this point to identify this ring with precision. The posterior half of the ring is more easily defined because of the prominent string like fibres of the puborectalis portions of the levator ani. The puborectalis, if followed forwards and upwards from behind with the rectal palpating finger, can be traced leaving the



ano rectal ring on each side of the anal canal to be inserted into the posterior surface of the pubic bones near the symphysis pubis

The *sphincter ani internus* can only be recognized apart from other sphincter muscles at its lower edge near the anal margin. It lies immediately under the mucosa and is palpated along almost the whole length of the anal canal. On withdrawing a long tubular rectal speculum from the distended rectum to the anal canal, the ano rectal ring contracts as the end of the speculum reaches the junction, and a narrow ring of mucous membrane appears. The highest portion of the internal hæmorrhoidal plexus lies just above the ano rectal ring.

### EXAMINATION OF THE RECTUM

Special preparation of the patient is not necessary for the local inspection of the rectum, as this viscus is usually empty, if fæces are present, it suffices to have them removed by a simple enema.

The posture most generally adopted for the examination of the patient is the left lateral. The buttocks are raised at the edge of the couch with the left elbow or arm placed behind the head the chest resting flat upon the couch and the knees well drawn up. Sometimes it is advantageous to place a sandbag under the left hip. This left lateral position is the most comfortable and least embarrassing when it is necessary to examine patients in the consulting room. Should the patient be very stout or particularly muscular, the adoption of the knee elbow position usually makes examination much easier. Before inserting any instrument, the external parts must be carefully examined, the condition of the skin noted, and search made for orifices of fistulæ. The anal margins should then be gently separated with the fingers to ascertain if any fissure is present, and digital examination continued with the first finger suitably lubricated. Vaseline is, as a general rule, more satisfactory than glycerin which is apt to cause pain. The examining finger, covered by a thin finger stall, will cause the minimum amount of pain and discomfort when carefully introduced. The front of the finger should be pressed towards the lateral wall of the anus, and then slowly inserted, so that lesions within the last  $\frac{3}{4}$  in of the bowel and any excrescences or indurations may be felt. Subsequently, the finger is passed up as far as possible to ascertain whether any further abnormality be present. It is necessary to note that internal piles usually *cannot* be felt, nor their extent estimated by means of digital examination. Many mistakes are made by a too rigid insistence that this can be done.

Local examination of the rectum and sphincteric region can be made by means of the anal speculum or endoscope. Lockhart Mummery uses a fenestrated speculum which is said to be the most satisfactory for the examination of fistulæ. This should not be rotated in order to examine a further portion of the anal canal, but should be withdrawn and re introduced. Another form of speculum is that known as the

modification of Kelly's short rectal tube. It should be warmed, well lubricated and gently introduced until the extremity has passed the sphincters. The obturator is then removed and, by means of a good head lamp, an excellent view of the rectum can be obtained and, on slow withdrawal, an equally good view of the anal canal. This is the best method for estimating the size and position of internal piles. For a more extensive examination, the sigmoidoscope is necessary.

### EXAMINATION WITH THE SIGMOIDOSCOPE

Indications for sigmoidoscopy may be summarized as follows —

- 1 Complaint of rectal pain, tenesmus, chronic diarrhoea, mucopurulent or blood stained stools
- 2 Hæmorrhage from the anus not attributable to hæmorrhoids
- 3 Constipation alternating with false diarrhoea
- 4 Chronic diarrhoea not yielding to medicinal measures
- 5 Blockage of the bowel due to some obscure condition

The rare contra indications to sigmoidoscopy are acute inflammations of the rectum, such as occur in acute bacillary dysentery, very acute ulcerative colitis, and conditions in which there may be acute inflammation of the peritoneum. Age and cachexia are also contra indications. To very nervous and hysterical people, and very sensitive women, a general anæsthetic may have to be given.

It is generally recognized that in practised hands accidents are very rare indeed and R. Bensaude, the well known author of monographs on this subject, records that none have happened in his experience.

**Instruments** — Many patterns of sigmoidoscope are now in use, but the one most commonly employed in English practice is Lockhart-Mummery's modification of the Strauss sigmoidoscope. This instrument is 30 cm long and consists of a tube which is closed posteriorly by a glass detachable window. At the posterior end there is a short tube to which inflation bellows can be attached, and some forms of instruments are provided with a handle. The illumination is obtained by means of a small electric bulb on a metal stalk, or holder, which, when in position is situated one inch from the anterior end of the instrument. By an ingenious arrangement the lamp may easily be removed for cleansing.

In order to insert the instrument with comfort, an obturator is provided, which is removed directly the muscular region of the sphincters is passed. The lamp is then introduced, the eye piece adjusted, and the further passage of the instrument controlled by sight. A smaller modification of the sigmoidoscope the proctoscope, which is some 15 cm in length, can be used for the inspection of the rectal canal.

Before using the sigmoidoscope, the operator must assemble the instrument and see that everything is in order, especially must he test the electric lamp, for failure in illumination at the critical

moment is extremely annoying. In these small electric bulbs, such failure may be brought about by trifling causes, which must be discovered. The strength of the current can best be tested by putting the terminals on the tongue, when the characteristic sensation is produced. Very often the defect is in the holder of the bulb itself, the wires of which may be freed by a pin.

Other instruments necessary in sigmoidoscopic examination are —

- 1 Long crocodile forceps such as are used for bronchoscopic examination (Patterson's bronchoscopic forceps)
- 2 A long probe for attachment of swabs which may be needed for bacteriological examination



Fig 1 —The author's long-handled Volkmann spoon for obtaining material from ulcers through the sigmoidoscope for microscopic examination

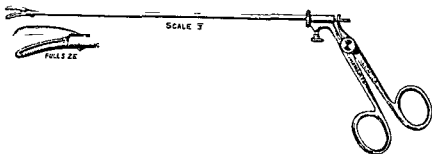


Fig 2 —Biopsy forceps for use with the sigmoidoscope

- 3 A long handled spoon on the principle of the Volkmann spoon, which the author employs to obtain scrapings of dysenteric ulcers for microscopic examination (Fig 1)
- 4 Forceps for obtaining pieces of tissue from the bowel for microscopic examination or biopsy\* (Fig 2)
- 5 An insufflator for blowing in medicated substances
- 6 A snare for removal of polypi (Lockhart Mummery's type)

The tube and obturator should be sterilized in boiling water before use, but the other parts of the sigmoidoscope should not be subjected to

\* The author favours the pattern manufactured by Vann Bros 63, Weymouth Street, London W

heit. They should be cleansed with spirit. The eye pieces require special care. Great help is obtained from a special magnifying eye piece, such as Wolfe's, which magnifies two diameters (at 30 cm) and which is the pattern the author prefers. For the study of the finer lesions in the bowel, and especially for the recognition of small amœbic ulcers, a magnifying eye piece is absolutely necessary. Fogging of the glass of the eye piece is prevented by warming before use, or lightly smearing with glycerin.

**Anatomical considerations** — Inspection of the rectum and the sigmoid loop would be very easy were the rectum a perfectly straight tube, but as it is not, the examiner must make himself familiar with the arrangement of the parts in order to guide the instrument skilfully. When the patient is placed in the genupectoral position, the rectum presents its perineal portion, 2-3 cm in length, directed horizontally forward, and then a second pelvic portion, measuring 9 cm, directed antero-posteriorly. The shape of the rectal ampulla itself is very variable.

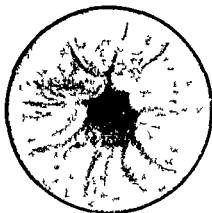
The interior of the bowel is not entirely smooth, for immediately above the sphincter there is a series of longitudinal folds known as the columns of Morgagni. The junction of the sigmoid flexure with the rectum is situated about 11-13 cm from the anus. The form of this loop may be compared schematically to the two arms of a V reversed so that in no case is it possible to see beyond 32-35 cm from the anus.

*The normal appearance of the mucous membrane and bowel* — In the normal subject the mucous membrane has a uniform rose or rose red appearance. If anything, it is paler in the region of the sphincter than in the ampulla. The practitioner should, however, beware of attaching too much importance to minor changes in the colour in the lower part of the rectum as aperients or enemata can influence the state of the mucosa. (Figs 3, 4, 5, 6)

The region of the ampulla is furnished with valves. At a distance of 7 cm from the anus two valves cross each other at right angles, the first of these is known as the valve of Houston, the second as that of Nélaton, or the coccygeal valve. In 28 per cent of normal people a third valve exists, the superior sacral valve. At 11-14 cm, the recto-sigmoid sphincter marks the entrance into the pelvic colon. This is more commonly known as the sphincter of O Beirne and it is always visible in the genupectoral position. It may be distinguished from the valves already mentioned by the fact that it disappears in the cadaver. When sigmoidoscopy is employed the presence of this valve is marked by a projection which simulates the os uteri, it is necessary to recognize this object, which is sometimes difficult to surmount. The sphincter having been passed the entrance into the sigmoid loop is seen to be marked by transverse folds. At 15-20 cm from the anus a region is reached where will be seen pulsations conducted from the internal iliac artery, and this appearance is most characteristic. Between 25 and

82 cm fall the limits of the ascending loop of the sigmoid and here well marked folds of mucous membrane are encountered

In performing sigmoidoscopy the operator should take note of the normal arrangement of the blood vessels which run parallel with the



3 Normal rectum in the region of the internal sphincter showing the plexiform arrangement of the submucosal blood vessels.



4 Normal rectum at 7 cm from the anus showing iliac branches on the right.



5 Normal rectum, upper portion, at 10 cm from the anus, showing a plexiform arrangement of blood vessels on the surface of the mucosa.



6 Entrance of the sigmoid at 15 cm showing the recto-sigmoid junction.

Figs 3-6—Normal appearances of rectum and sigmoid as seen by sigmoidoscopy  
(Partly after Zimmon)

folds of the mucous membrane. In inflammatory states of the mucous membrane itself the contour of these vessels may be obscured. It is just as important to take note of the changes in the blood vessels of the intestinal mucosa as it is to observe the minor vascular changes

in the fundus oculi and this can only be satisfactorily performed by a magnifying eye piece

The characteristic and diagnostic appearances of the various pathological conditions described will be found in the appropriate sections of each disease

**Hæmorrhoids** — These are generally easy to distinguish but they rarely have the classical appearances described in text books. They normally appear red violet sometimes the actual outlines of the veins can be seen but their presence can usually be ascertained by the violet discoloration underlying the mucosa and there may be venous varices simulating ecchymoses. When the hæmorrhoids are inflamed a hæmorrhagic rectitis is produced and the patient may appear pale and cadaverous suggesting carcinoma. More rarely venous dilatations may be seen in the rectal ampulla when they are not visible in the sphincteric region. Accompanying this hæmorrhoidal state the anal papillæ just above the external sphincter on the borders of the muco cutaneous junction are usually hypertrophied giving a crenated appearance.

**Preparation of the patient** — For a satisfactory examination it is essential that the lower bowel should be entirely free from fæces and to ensure this practitioners adopt various methods. It is seldom possible to examine a patient suitably without some form of preparation unless the bowels have been naturally well emptied just previously. Methods of cleansing the bowel vary according to the condition of the patient whether constipated diarrhœic or normal. Usually it is necessary to inject a pint or more of hot water three to four hours before the time fixed for the examination and to continue lavage till the effluent is perfectly clear. In cases of severe constipation strong cathartics must be used with caution because their action may be continued during the examination flooding the bowel with liquid fæces.

Not later than 2 p.m. on the day before the patient should be given  $\frac{1}{2}$ – $\frac{3}{4}$  oz. of castor oil and lavage of the rectum should be performed on the morning of the examination. Should the patient be suffering from diarrhœa then the preliminary aperient must be omitted 5–15 minims of tincture of opium being given half to one hour beforehand. If the diarrhœa be very severe an injection of  $\frac{1}{4}$  gr. of morphia is much more satisfactory. As a routine the author finds it advantageous to dull sensation by giving 1–2 gr. of luminal half an hour before instrumentation which then becomes practically painless.

It is essential that the preparation should be conducted in a hospital or some institution where there are trained nurses because if left to themselves patients invariably take the enema too late. The patient must always be instructed to pass urine immediately before examination.

Some authorities prefer to examine the bowel without any preliminary preparation claiming that the mucous membrane will then best be seen in its natural state. This is the practice at St. Mark's Hospital in London.

The examination itself is best performed on a properly constructed table. If such a table is not procurable, an ordinary operating table provided with lithotomy stirrups is a useful substitute.

**Position of the patient**—The position in which the patient is placed for sigmoidoscopy is very important. Undoubtedly the genupectoral position is the one most favourable from the operator's point of view, as the rectum and pelvic colon then fall more or less into a straight line, and the instrument can in most cases be inserted directly into the bowel without the aid of inflation. But in practice this position has not been found acceptable to the majority of British patients. Moreover, in elderly people and those who are cachectic or otherwise in bad health it is apt to cause giddiness and faintness. When a special sigmoidoscope table is provided it is possible to arrange the patient lying on his abdomen with his head directed towards the floor. This position has the same advantages as the genupectoral. The dorsal posture with the knees raised, i.e., the lithotomy position is the one most usually employed, being the most convenient for the patient. It has the disadvantage that sometimes considerable inflation of the bowel is required to enable the sigmoidoscope to be passed and also that considerable skill is often needed to direct the instrument round the various bends. The Sims dorso lateral position where the patient is placed on his right side with the buttocks elevated on sand bags facing the operator, and with the knees drawn up, has the advantage of being much less fatiguing, and is therefore more suitable for prolonged examination or where the patient is in a feeble state of health. It is the position most favoured by the patient. The vertical position of Grinnville S. Hanes in which the patient is literally standing on his head has been used for high sigmoidoscopy especially in America, but it is quite unsuited for any but the most robust.

**Technique**—As already stated before sigmoidoscopy, a digital examination of the anus itself must always be made otherwise important lesions may be missed. A well lubricated examining finger also facilitates the introduction of the instrument. When the anus is excoriated a suppository of 2 per cent cocaine should be inserted and if there is a fissure 20 c.c. of 2 per cent novocain solution should be injected into the rectum. Before use the sigmoidoscope tube should be placed in warm water and warmed to a temperature agreeable to the hand, it must be remembered that the anus is extremely sensitive to heat. The tube itself should be well lubricated with vaseline or, better still with a glycerin antiseptic known as K. Y. Jelly (Johnson & Johnson).

With gentle pressure the sigmoidoscope with its obturator, is inserted into the anus and gradually the resistance of the sphincters is overcome. It is important to note the actual resistance of the sphincters as this has a bearing on the diagnosis. After the instrument has entered to the first 5 cm, the obturator should be withdrawn, the

light inserted and further passage through the lumen of the bowel guided solely by sight. In the genupectoral position the passage is easy and insufflation is not required, but in the dorsal and lateral positions inflation is essential, the necessary pressure on the bulb should be made by the operator himself, who should instantly release it should the patient complain of acute pain. After passing the sphincter region, when the patient is in the lithotomy position, the instrument is held horizontally, and then directed upwards and backwards in the direction of the rectal ampulla. At 11 cm it must again be directed in a horizontal direction so as to find the entrance of the pelvic colon. This loop is not usually situated medially, and is directed towards the left more often than to the right. Again the direction should be at first horizontal and then vertical, until the entrance to the loop is secured. This is by no means always easy, and frequently the operator has to withdraw the instrument for a short distance, at the same time making the patient inspire deeply. The spontaneous ejection of faecal matter, mucus, and sometimes gas may mark the exact spot to which the opening of the instrument should be directed. Only as a last resource should energetic insufflation be employed. S. B. Kleiner (1930) compares the introduction of the sigmoidoscope into the bowel to a football game, in which every breath of air provides interference and the operator follows this interference just as the player, carrying the ball, looks for an opening space into which he may plunge.

When the descending branch of the pelvic loop is penetrated the operator must manipulate the instrument and insufflate the bowel. It is necessary always to keep the lumen of the intestine in the centre of the field of vision as the instrument is advanced. This is as far as one can safely proceed, and at this stage it should be possible to palpate through the abdominal wall the extremity of the sigmoidoscope as it lies in the sigmoid flexure (Fig 7).

Now the instrument should very gently be withdrawn and the examiner can observe minutely the folds of mucous membrane as they present themselves. More important observations upon the position and character of intestinal lesions are made during retraction of the instrument than upon its introduction and, moreover, this retrograde inspection has the great advantage of permitting the examination of the whole sphincteric region which was originally traversed by the instrument obstructed by the obturator.

In order to cleanse the bowel, some pledgelets of cotton wool are introduced in the crocodile forceps, and they may also be employed to remove an excess of fluid or liquid faeces. Water syphonage can also be adapted and the apparatus may be attached to the nearest tap, this is often extremely useful when the bowel contents are copious and offensive. Besides rendering the lumen of the bowel patent, insufflation has other advantages, it may be employed to delineate the outlines of a tumour or to test the elasticity or otherwise of the mucosa. In normal conditions the natural folds of mucous



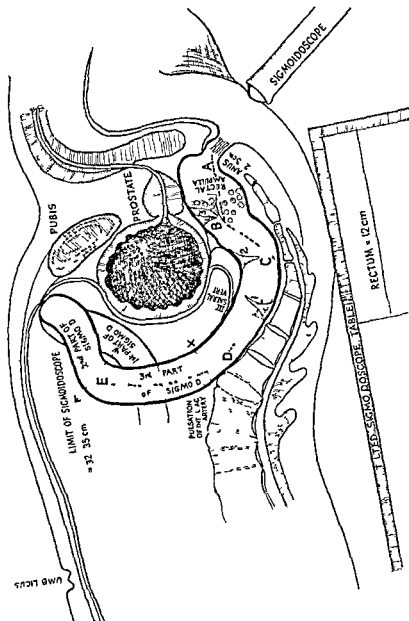


Fig 7 —Diagrammatic scheme of rectum and sigmoid for use in sigmoidoscopy

Dotted line — position of sigmoidoscope when patient in lying position. A B horizontal B C, backward (or posterior) C D and horizontal D L vertical (or forwards) I = 2 valves. III sacral vertebrae, the recto-sigmoid junction (sphincter of O B rect) The small circles (with dot) indicate the common situation of amoebic ulceration at 5 cm.

membrane are rapidly reduced under gentle insufflation and re-form again the moment the pressure is relaxed. In marked contrast, when the mucous layer is infiltrated with inflammatory exudates, the folds disappear and reappear again far less readily, so that greater force is necessary to introduce the instrument and this itself causes pain, thus, in the inflammatory states, sigmoidoscopic examination is more painful than when simple ulcerative lesions are present. A certain amount of skill is required in controlling the forces of insufflation, and usually beginners overdo this process, thereby causing unnecessary pain and inconvenience.

The distance that can be attained with a sigmoidoscope depends, firstly, upon the skill of the operator and secondly, upon the anatomical conformation of the colon. The examination of the sigmoid region is much easier when the meso sigmoid mesentery is long. In some patients it is almost impossible to enter the loop without giving a general anæsthetic. Where an intestinal tumour can be felt in the abdomen its examination by sigmoidoscopy is most necessary before the surgeon can proceed to laparotomy.

Sometimes the walls of the intestines being abnormally dry and lacking in mucus, cling to the sides of the instrument like the fingers of a glove, sometimes, also, the walls of the bowel become stretched over the upper end of the sigmoidoscope like a drum, and when undue pressure is made by the operator in these circumstances perforation of the bowel may occur. This is specially likely to take place when the bowel wall is weakened or attenuated by a prolonged ulcerative process.

Radiography can be employed to determine the extent to which the instrument has been passed, and it is surprising to see the position in which it may lie in the abdomen thus demonstrating the variation in the anatomical position of the sigmoid flexure. The extremity may even be found in the epigastric region or abutting the lower edge of the liver.

The routine employment of the sigmoidoscope should not encourage the examiner to neglect the older methods of examination. The education of the sense of touch is most important. There are many instances of small circumscribed cancers of the rectum (8-10 cm above the anus) which can be accurately palpated by the finger and the diagnosis made with certainty, when they may not be easily visible through the sigmoidoscope. There are amœbic and tuberculous lesions which superficially resemble carcinoma very closely and may be distinguishable only by means of touch. Carcinomata of the posterior wall of the rectum, which may be tucked away and hidden in the concavity of the sacrum may easily be passed over by the instrument without being seen, and sometimes infiltrated malignant glands may be felt through the rectum when no visible lesion can be detected.

In certain conditions palpation alone may give rise to errors. This

is specially so in the case of internal hæmorrhoids which cannot be felt and can only be seen, and which when thrombosed, may, unless seen be mistaken for solid tumours. It is often necessary to use sigmoidoscopic in association with radiological methods, but it must be confessed that in the minor changes of the rectum radioscopy is not only disappointing, but fallacious. Finally, reliance must not be placed upon sigmoidoscopy alone to the exclusion of other methods of examination, such as the microscopic examination of the fæces and palpation of the abdomen.

In the following table a summary is given of some of the practical results of routine sigmoidoscopy, to which future reference will be made.

TABLE III—STATISTICS

Number of dysenteric cases examined by sigmoidoscopy in the Hospital for Tropical Diseases 1920-1937 to ascertain the frequency of stricture in tropical practice 3068

<i>Stenosis and stricture of rectum (incidence 0.8%)</i>	27
Chronic bacillary dysentery	7
Chronic amœbic dysentery (including pericolic abscess)	5
Ulcerative colitis	2
Tuberculosis of colon	2
Syphilitic stricture	1
Gonorrhœal proctitis	1
Polypous	1
Lymphogranuloma inguinale	2
Diverticulitis	1
Carcinoma of rectum (post dysenteric)	5

## CHAPTER III

### HISTORICAL SURVEY OF THE DYSENTERIES

DYSENTERY, or the 'bloody fluxe' of our forefathers, has been an object of curiosity and study since the earliest times. It is now fairly certain that Hippocrates, the Father of Medicine, distinguished it as a disease distinct from other forms of diarrhoea and that he noted the significance of tenesmus a symptom which supervened frequently in cases of mortification. Aretæus, Celsus Archigenes Galen Caelius Aurelianus and Alexander von Tralles all give somewhat crude clinical descriptions of dysentery. Celsus in particular ascribed the bloody fluxe to ulcers in the interior of the intestine which caused the patient to suffer continuously from tenesmus and pain near the anus.

These ancient writers, however, appear to have described only sporadic forms of the disease, it was from the fifth century onwards that epidemics were noted in Europe. The chroniclers of the period record epidemics of dysentery in France in A.D. 534 and 538 and again in Northern Europe in A.D. 760.

The infectious nature of the disease was first referred to by Fabricius Hildanus in 1646, shortly afterwards ipecacuanha was introduced from Brazil as a specific for dysentery and the drug became known hence forward as the "dysentery root". Jacobus Bontius, the 'grandfather of Tropical Medicine,' in 1642, described a great epidemic of dysentery which raged in Java in 1628, and apparently he himself suffered from the disease during the siege of Batavia, which he so feelingly depicts. The true dysentery, Bontius writes, is an ulceration of the intestines with a perpetual purging, at first mucous and afterwards bloody, and lastly purulent with intolerable pain and griping of the belly. Bontius ascribed the epidemic to the defilement of the air and drinking water by the dead bodies of men and animals and to the water being polluted by the roots of *Serpentaria*.

In the middle of the seventeenth century the subject of dysentery figured much in medical writings, especially in those of Sydenham Morton and Willis concerning the great epidemic of 1668-72. They first distinguished clearly between blood stained dysentery stools and a pure mucous evacuation and apparently recognized the association of arthritis with dysentery. Willis regarded dysentery as a recurrent annual evil, while Morton considered that it constituted an expression of intermittent fever. By the middle of the next century, John

Pringle had given accurate accounts of dysentery in the English Army, and G. Cleghorn in the English Fleet off Minorca. Pringle (1752) fully realized that epidemic dysentery constituted a single entity, and that it was an infectious malady conveyed by the discharges of the patient. In 1767 J. G. Zimmermann wrote a book on the dysentery epidemic he had observed in Switzerland and gave an accurate description of the clinical varieties of the disease.

During the first half of the nineteenth century the theory still prevailed that dysentery was but one expression of malaria, so that it remained for Cruveilhier, Rokitsansky and Virchow, by patient and exact observations to put the pathological processes of the disease on a more secure basis.

The resemblance of dysentery to malaria in its tendency to break out at long intervals in pandemic form extending over tracts of country, impressed many observers notably Hirsch (1886) until recent times.

Such epidemics were noted in the United States in the years 1749-53, 1773-77 and 1793-98. In France it raged in 1749-50 and again in 1759, especially in the Central and Southern provinces. In Switzerland a pandemic occurred in 1659. In Holland in 1556 and 1621, in Belgium in 1891 and in Luxemburg in 1863.

In 1740 dysentery was noted over a large part of England, and again in 1668-72. In Ireland there are records from 1728-30, and it appears that dysentery was associated with typhus in the famine years of 1817-18 and again six years later. In Marlborough's days dysentery was so common in Ireland that it was known as the 'Country Disease', and at the siege of Dundall in 1689 there were 6,000 deaths from this cause. In Germany it was widely spread—for instance, in 1676-78 it occurred in Saxony and the Rhine Provinces and in 1726-28 in Silesia, Saxony and the Mark of Brandenburg. In Sweden, 1649-52 it raged over nearly the whole country, and in 1770-75 in nearly every province. Similar conditions were noted in the southern districts of Norway 1808-10. In Italy there is one instance in 1787, of an epidemic which spread widely throughout the land.

One of the most extensive and malignant of dysentery pestilences in the central parts of Europe occurred in the years 1834-36. In France the disease had shown itself in 1834 in many of the Northern districts including Brittany and the department of Maine et Loire, and in 1836 it broke out again over a large part of Northern, Eastern and Central France. It was in Germany, however, principally in the South and West that dysentery in those years acquired a truly pandemic character. According to a table compiled by Hauff the death rate there was very considerable in 49 places attacked. In Neckar there were 9,777 cases with 1,000 deaths, and it is said that more than 14 in every 1,000 inhabitants perished.

Telling evidence of the relationship between circumstances adverse to health and well being and the occurrence of dysentery and diarrhoea is furnished by the breaking out of this disease as a sequel to war and

famine The war-pestilence of Athens during the Peloponnesian War has been paralleled by experiences during the nineteenth century

The Wars of Napoleon 1790-1815 the Crimean War, 1854-55, the Franco German War, 1870-71, the Russo Turkish War, 1878-79, the English Campaign in New Zealand, 1860-61—in the Eastern Hemisphere and in the Western—the French occupation of Mexico, the Secession War in the United States, have proved repeatedly that dysentery must be placed with typhoid and typhus among the foremost pestilences of war

Famine and sickness consequent on failure of crops were responsible for dysentery in Ireland in 1806, 1817, 1821, 1826, and 1846-7, in Tobolsk, Russia, in 1863 and in Upper Senegambia, Africa, 1853-55 Smaller outbreaks are recorded in Iceland in 1850, where the disease broke out in consequence of bad food Outbreaks of dysentery tended to occur in prisons, barracks, and institutions of those kinds, and among the poorer classes of the people, and among the rural population rather than the urban

#### A SURVEY OF THE LITERATURE OF DYSENTERY IN TROPICAL REGIONS

Although dysentery in its varied manifestations was well known in Europe during the Dark Ages, it was only towards the close of the eighteenth century that attention began to be drawn to this disease in the tropics, where the mortality it occasioned was appalling

The Spanish Wars and Elizabethan enterprises had secured an enduring heritage for Great Britain in the West Indies, and here, among the negro slaves, the British garrison, and the fleets which cruised the Caribbean Seas, epidemics of dysentery were studied and treated by an almost bewildering variety of remedies In the writings of the naval and military surgeons we find a tendency to differentiate forms of dysentery on purely clinical grounds, but it is to a practising physician, James Grainger, of St Kitts, that credit must be given for distinguishing, in an essay on "The More Common West India Diseases and the Remedies which that Country Itself Produces," (1764), two fundamentally distinct types, in this manner anticipating the East Indian physicians by nearly forty years From the clinical description of West Indian dysentery in "Observations on the Changes of Air and Concomitant Epidemical Diseases in the Island of Barbados," by W Hillary (1759) and "Observations on the Acute Dysentery" by John Rollo (1786), it is safe to assume that the dysentery they had encountered was of the bacillary type

To vapours, humours, and other malign influences put forward as causes of dysentery can be added the "obstructed perspiration" theory advanced by Benjamin Moseley (1787) in "A Treatise on Tropical Diseases and on the Climate of the West Indies" James Trotter, in 1804, describing an epidemic that occurred in the Jamaica fleet after a great hurricane, ascribed its cause to the drenching of

bedding in sea water in conjunction with the effects of fatigue and salt provisions. That this particularly fatal epidemic was probably bacillary dysentery may be gauged from his frequent references to stranguary or *dysuria dysenterica* a frequent and disagreeable accompaniment of the infection. The first mention of dysenteric rheumatism in modern times is made by William Harty in 1805. To the horrors of the slave trade at this time must be added the effects described by Thomas Winterbottom (1803) of dysentery amongst the human cargo out of 700 slaves shipped at Sierra Leone only some 380 lived to see Barbados. The first mention of drinking water as the infective agent in the West Indies is made by James McCalo in 182.

Mention must also be made of the work of the great clinical physicians in India thus James Johnson who studied tropical diseases in his world wide wanderings published his experiences in *The Influence of Tropical Climates on European Constitutions* in 1813 an account later supplemented by Sir James Ranald Martin (1856) a Fellow of the Royal Society and erstwhile surgeon on the Bengal Medical Establishment of the East India Company. Undoubtedly the greatest work on dysentery in the early part of the nineteenth century is contained in Sir James Annesley's (1828) *Researches into the Cause Nature and Treatment of the more Prevalent Diseases of India*. In one section he gives a remarkably accurate pictorial and verbal illustration of liver abscess and the appearances of the large intestine in both forms of dysentery. To Sir George Ballingall in a work on the diseases of European troops in India must be given credit for differentiating in that country the two distinct clinical types of dysentery, now known as amœbic and bacillary.

Other works of this period which deserve brief notice are the *Clinical Illustrations of the More Important Diseases of Bengal* by James Twining in 1852. *Researches upon the Diseases of India* by Charles Morehead (1856) and a *Commentary on the Diseases of India* by Norman Chevers in 1886.

But now a new era opened up an era connected with the establishment of verifiable facts an era connecting a tangible ætiology with the ascertained pathology. In 1855 at Prague W. Lambl found living amœbæ in the fæces of a case of infantile diarrhoea. This was the first step it was not until 1875 that a further great advance was registered. Then F. Lösch in St. Petersburg again found these organisms in a case of chronic dysentery and by injection of the dysenteric material into the rectum of four dogs found that dysenteric symptoms developed with rectal ulceration in which amœbæ were proved to be present.

Those who gaze at the original drawings of this pioneer in Virchow's *Archiv* for 1875 will have little difficulty in convincing themselves that Lösch's amœba was indeed *Entamoeba histolytica*. Less satisfying are the figures of D. D. Cunningham (1870), who found amœbæ commonly present in choleraic stools in India. The work of the latter,

however gained added authority through the investigations of Robert Koch in 1883 in Alexandria and in India he again found these organisms in choleraic stools and also in sections of the human intestine.

Fired by the work of the master bacteriologist S. Kartulis in Egypt recorded amœbæ in the fæces of 500 patients suffering from dysentery and also in liver abscess pus and in the walls of liver abscesses. Soon afterwards confirmation came from the New World in 1890 W. Osler of Baltimore demonstrated amœbæ in a case of dysentery with liver abscess originally contracted in Panama.

Then in 1893 W. Kruse and A. Pasquale again in Egypt first put forward the novel suggestion of two species of amœbæ one harmless and the other pathogenic and they proceeded to prove their contention by producing dysenteric lesions by means of the intrarectal injection of cats with dysenteric stools and liver abscess pus. Another ten years then elapsed before the appearance of Schaudinn's historic paper wherein he traced the life history of the human intestinal amœbæ christening one *Entamoeba coli* and the other the pathogenic form *Entamoeba histolytica*. In the meantime the differentiation of the epidemic from the more chronic form of dysentery was definitely established by the discovery and isolation of the dysentery bacillus by K. Shiga in Japan in 1898.

The history of the specific remedies employed in dysentery is almost as romantic as that of the causes of the disease.

The use of ipecacuanha is a case in point. This drug is the root of *Psychotria ipecacuanha* a small plant from Brazil. This is the official root and is known as Rio ipecacuanha that from Colombia is distinguished as Cartagera ipecacuanha. The first mention of ipecaca as a remedy for the bloody flux is made by a Portuguese friar and is published by Samuel Purchas in 1625 in Purchas his Pilgrimes. \* the use of this drug by the Indians is there discussed. After this time ipecacuanha or the dysentery root came into more common usage. It is referred to in the work on the natural history of Brazil (1648) by Piso and Marcgraf who described the plants to which the name was applied.

Although the drug was in common use in Brazil it does not appear to have been brought to Europe until 1619. It was prescribed by Helvetius a Dutch physician practising in Paris from whom the French Government bought the secret in 1688 paying £800 for it.

The use of ipecacuanha in dysentery was strenuously advocated by the great James Lind (1768) although it appears to have been introduced into general practice in the West Indies in 1726 by Richard

#### \* FOR THE BLOODY FLUXE

Ipecaca or Iugava is profitable for the bloody fluxe the stalkes a quarter long and the roots of another or more it hath onely foure or five leaves it smelleth much wheresoever it is but the smell is strong and terrible this roote beaten and put in water all night at the dew and in the morning if this water with the same roote beaten and strained be drunke onely the water it causeth presently to purge in such sort that the laske ceaseth altogether.



Towne who gives minute instructions for its exhibition, which he modestly ascribes to the "learned and judicious Dr Friend"

James Sims (1773) in his "Observations on Epidemic Disorders," recommended two methods of exhibiting "ipecoanha" in dysentery, in so large a dose as to promote emesis, or, better still, in smaller doses with opium. He was a pioneer in another respect also, in that he insisted on the value of this treatment in the chronic (or amebic) form of the disease. In Thomas Trotter's "Medicina Nautica" (1804) another method of ipecacuanha treatment was given, employing 12-15 gr doses daily. Its chief merit was its emetic action in discharging the contents of the stomach.

Subsequent to the writings of these pioneers, the use of ipecacuanha became more general and is frequently mentioned by the older generation of Indian physicians. Patrick Manson shared to the full the belief of his predecessors in the sovereign value of ipecacuanha, and employed it exclusively in his practice from 1893 onwards. He recognized its efficacy not only in chronic dysentery, but also in liver abscess, and he evolved a technique of his own for its administration.

Almost as numerous as the speculations on the origin and nature of dysentery have been the variety of remedies suggested for its cure. Antimony oxide, in the form of James's powders\* was recommended by Robert Jackson in 1817 and by numerous other writers. The use of opium has always been popular and a belief in its curative power has persisted almost to the present day. In 1796, C Maclean used it in enormous doses in combination with calomel, and George Cleghorn (1751) was a firm advocate of opium for the ship dysentery of his day. Ascalm (1801) dilates upon the "sovereign powers of opium" and the soothing effects of anodyne fomentations and tepid baths. Thomas Clark (1801) advocates the exhibition of 3-5 gr of James's powders\* with an addition of a few drops of laudanum to promote perspiration.

The more modern treatment by the purgative action of saline aperients appears to have been adumbrated by Donald Monro (1780). In his opinion the important part of the cure depended on the use of gentle purges at the beginning of the illness to carry off the corrupted humours, the purgative being repeated every second, third and fourth day as the case required. Rhubarb was advised, although not so efficacious as saline purges.

John Rollo (1786) was a wholesale admirer of the laxative treatment, which he persisted in giving through the whole course of the disease. James McCabe (1825) was the first to employ charcoal extensively. Norman Chevers favoured the bael fruit in chronic dysentery, and also initiated the era of calomel in large doses (10 gr or more). Gradually from the tendency to employ cathartics, we see the development of the modern aperient treatment of bacillary dysentery.

\* JAMES'S POWDERS.—Antimony oxide 33 per cent and precipitated calcium phosphate 67 per cent. The dose is 3 gr U.S. National Formulary. There is a history of James's powders by Michael Donovan in the *Pharm. J.*, 1867.

## CHAPTER IV

### GEOGRAPHICAL DISTRIBUTION OF THE DYSENTERIES

**Great Britain. *England***—That bacillary dysentery exists in an endemic form and that sporadic cases of this disease occur from time to time is now well established. Dysentery has played its part in English history. Edward I died of relapsing dysentery in 1307 and Henry V of this disease in 1421. In recent years too, small epidemics of bacillary dysentery have been recorded. It is probable that dysentery bacilli are normally present in a small proportion of the population, and the more general recognition of this disease is due to increasing knowledge and more careful investigation of patients suffering from diarrhoea.

A. S. MacNalty reported two outbreaks of acute dysentery in London (Chelsea and Islington) during the autumn of 1917. It was considered that a close connexion with antecedent cases could be traced, and the prevalence of dysentery of the same type in the Army in France was held responsible for its introduction into London.

G. S. Buchanan (1918) reported an outbreak of Shiga dysentery in an institution in the Eastern Counties, in which 38 cases were recorded with two deaths. Flexner outbreaks have also been noted by A. G. M. Severn and E. N. Evans in Smethwick, in August, 1927, and by J. A. Charles and S. H. Warren (1929) in Newcastle upon Tyne, between March, 1928 and June, 1929. The infection was mostly of the Flexner type and they conclude that it is a relatively common disease, this has been borne out by recent experiences.

**Scotland**—T. A. Pratt and H. W. O. Frew (1930), in a clinical account of an outbreak in Glasgow in October, 1929, report that out of 25 cases, 19 were due to the Flexner bacillus. According to A. M. Fraser and J. Smith (1930), bacillary dysentery has existed in Aberdeen since 1919, and between that date and 1928 they recorded 147 cases of Flexner infection. No cases of Shiga infection were found.

**Wales**—A report made by T. W. Wade for the Ministry of Health describes an outbreak in the Ogmore Vale, Glamorganshire, in May, 1921, in which it is estimated that some 1,100 persons suffered from mild dysentery. The outbreak followed a severe drought and was limited to a defined area, and evidence showed that houses situated near the source of the water supply were more seriously affected than those more remote. Three hundred and twelve cases attended by

local practitioners were distributed in 148 houses and no less than 32.9 per cent of the occupants of these houses were attacked. There were 12 deaths during the height of the epidemic—five in infants under one year of age. The outbreak was due to a Flexner bacillus of the W type.

*Ireland*—In August 1919, A. Stokes and J. W. Bigger described an epidemic of bacillary dysentery in Dublin, the first recorded in modern times. In all 186 cases with 19 deaths were notified and out of 189 patients whose faeces were examined bacteriologically, the dysentery bacillus (for the most part Shiga) was isolated in 59.6 per cent. No special difficulty was experienced in isolating or identifying the organisms.

*India*—So many references will be made to dysentery in India in subsequent pages and so much of first rate importance has been written upon the aetiology of the disease in that country, that an elaborate account cannot be undertaken here. As to the true relationship of one form of dysentery to the other, it is very difficult indeed to form a just estimate since the methods of diagnosis and the statistics set forth have varied so much from time to time.

In the summaries recorded in the League of Nations Report for 1930 for the whole of India a bacillary diagnosis was made in 64.6 per cent, among both British and Indian troops. The proportion of amoebic dysentery was given as 8.4 per cent among the Indian troops and 15.6 per cent among the British.

In most of these cases the diagnosis was confirmed by a laboratory test but in 46 per cent of cases attributed to bacillary dysentery, no dysentery bacilli were isolated, the only indications being the clinical diagnosis and the cellular exudate in the stools. The bacillary types were distributed as follows: Flexner 77.6 per cent, Shiga 15.7 per cent (responsible for most of the deaths); and Sonne, 2.2 per cent.

It is instructive to note the successive and rather puzzling alterations that have been recorded in the military statistics of dysentery in India during the last fifteen years. From 1920 to 1925 a large majority of the cases were attributed to the amoebic form (for probable reasons, see p. 45). From 1925 onwards the pendulum swung in the other direction and it was the bacillary forms or cases clinically like them which prevailed and these still prevail in the proportion of six to one. There is little doubt that this remarkable change is due to better laboratory facilities and more accurate appreciation by the pathologists of the intricacies of this subject.

The experiences of J. A. Manifold (1926) on important features in the correct diagnosis of dysentery in India and the use of this worker with A. J. De Monte (1929) require special mention. In 1926 a searching investigation was undertaken by them on the dysenteries of Poona where previously the main form of the disease had been thought to be amoebic. The figures they published have entirely reversed the proportion which the two main forms of dysentery held to one another.

In nine months of that year there were 310 cases of bacillary dysentery and only 13 cases of proven amœbiasis

It is worthy of note that J Cunningham (1923) found that 86 per cent of the dysentery in the jails of Eastern Bengal was bacillary and that the percentage was the same among the prisoners in the Moplah rising in the Madras Presidency, H W Acton and R Knowles found in 1920-23, that, in Calcutta, bacillary dysentery was at least five times as common as amœbic

The appended tables are taken from the Report on the Health of the Army for the year 1935 (Vol 71) Further comment is unnecessary

TABLE IV

NUMBERS OF CASES DIAGNOSED DYSENTERY, DIARRHŒA, AND COLITIS DURING PERIODS 1920-1925 AND 1930-1935

	British Other Ranks				Indian Other Ranks			
	1920-1925		1930-1935		1920-1925		1930-1935	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Bacillary dysentery	402	10	540	3	411	9	7892	17
Amœbic dysentery	3176	25	1079	0	3272	47	814	1
Clinical dysentery	497	7	1987	1	4281	74	2767	11
Diarrhœa	5878	0	4900	0	14627	8	5063	0
Colitis	1420	2	187	0	15492	42	167	2
Total	11,373	44	11,683	4	37,206	180	16703	31

The extraordinary contrast in the diagnoses, the large reduction in the number of deaths and the slight increase in admissions among British troops, as compared with the huge fall in total admissions among Indian troops can perhaps be better appreciated if only the difference in admissions between the two periods are observed, as in Table V

TABLE V

TOTAL ADMISSIONS FOR DYSENTERY, DIARRHŒA AND COLITIS DURING 1930-1935 CONTRASTED WITH THOSE DURING 1920-1925

	Bacillary dysentery	Amœbic dysentery	Clinical dysentery	Diarrhœa	Colitis	Total admissions for group	Deaths
British troops	+ 5068	- 209	+ 1490	- 918	- 1223	+ 2,118	- 49
Indian troops	+ 7632	- 459	2,554	- 8,592	- 25,378	- 25,773	- 222
Total	+ 12700	- 668	- 1064	- 9510	- 26,601	- 23,655	- 271

The distribution of Sonne dysentery is dealt with in the section devoted to that subject (p 68)

## CHAPTER V

### DYSENTERY : CLASSIFICATION

It is always a matter of difficulty to define exactly what is meant by the term 'dysentery,' mainly because many phases of the diseases included under this heading are not characterized by dysenteric symptoms as generally understood. The term "Dysentery" is derived from the Greek *dis* (beyond) or *contra* (against) (a bowel complaint) and this definition if properly appreciated, explains the main outstanding symptoms. To the popular mind it indicates passage per rectum of blood stained mucus derived from the bowel wall. The passage of these abnormal intestinal contents is attended by generalized abdominal pain or discomfort and is usually accompanied by tenesmus or straining.

The term dysentery has become applied to a symptom complex which, as modern research has revealed may be produced through the infection of the bowel itself, or the invasion of its walls by many different organisms. Thus it can readily be realized that diagnosis of the dysenteries and consequently their treatment may become a very recondite and intricate problem. It must be remembered that diseases essentially of wide and distinct ætiology may resemble each other closely in outward appearances and hence it becomes necessary to correlate as has been attempted in these pages, the clinical, pathological, bacteriological, and protozoological aspects before an expert opinion can be given on any individual case.

It is customary and indeed convenient to classify the dysenteries by dividing them into main headings according to whether they are of bacterial, protozoal, or metazoal origin. The following classification has therefore been evolved —

**Bacillary or Epidemic Dysenteries, caused by the dysentery bacilli —**

- (i) Shiga's bacillus (*B. dysenteriae* Shiga Syn. *Eberthella dysenteriae*)
- (ii) Schmitz's bacillus (*B. dysenteriae* Schmitz)
- (iii) Flexner's bacillus (*B. dysenteriae* Flexner Syn. *Eberth para dysenterica*)
- (iv) Sonne's bacillus (*B. dysenteriae* Sonne \* probably identical with *B. dispar* (Andrews))

\* Also known as the Kruse-Sonne bacillus.

**Protozoal or Endemic Dysenteries.**

(a) AMŒBIASIS, or infection with the dysentery amœba (*Entamoeba histolytica* (Schaudinn))

This term includes.—

1. Primary intestinal amœbiasis or "amœbic dysentery"

2. Secondary amœbiasis (complications of 1)—hepatic amœbiasis, amœbic liver abscess, etc.

(b) BALANTIDIASIS, or infection of the intestinal canal with an infusorian, *Balantidium coli*. This is a rare infection, but is quite commonly found in lower animals

(c) COCCIDIOSIS, infection with *Isospora hominis*, a rare infection of the intestinal tract of man about which little is known

(d) GIARDIASIS, or lambliasis, an infection of the small intestine with *Giardia intestinalis*, a protozoan flagellate

(e) FLAGELLATE DIARRHŒA, or infection of the intestinal canal with protozoan flagellates—*Trichomonas hominis* and *Chilomastix mesnili*. This is a rather doubtful pathological entity

(f) MALARIAL DYSENTERY, occurring in the course of infection with *Plasmodium falciparum*

(g) LEISHMANIAL DYSENTERY, occurring in the course of kala azar (*Leishmania donovani*), usually a terminal event

**Metazoal or helminthic dysenteries**—A dysenteric syndrome brought about by ulceration or inflammation of the intestinal tract by helminths, of which *Bilharzia* is the most important. The eggs of these parasites, in passing the intestinal walls, give rise to ulceration and papilloma formation which in turn cause dysenteric symptoms. Other species of helminths also may give rise to similar symptoms

## **The Bacillary Dysenteries**

## CHAPTER VI

### THE BACILLARY DYSENTERIES

**Synonyms.**—Acute or epidemic dysentery

*French* Dysenterie bacillaire

*Italian* Dissenteria bacterica

*German* Bazillenruhr

*Japanese* Ekin

**Definition** —A group of infectious diseases caused by invasion of the colon, and occasionally also of the ileum, by bacteria of dysentery occurring sporadically or in epidemic form. The principal feature of the disease is the passage of frequent blood stained stools, or exudate consisting to a great extent of blood and mucus without faecal contamination. Usually pyrexia, griping, and tenesmus are present in varying degree. An outstanding clinical feature is intoxication due to absorption of dysenteric toxins. This condition may become chronic and lead to chronic bacillary dysentery. The most frequent complication is inflammation of the synovial membranes.

#### ÆTIOLOGY

Predisposing causes include unsuitable food, exposure to extreme heat or cold, errors of drink and diet and fatigue, especially during exigencies of military service, and these must all be taken into consideration. In tropical regions irritation of the bowel by foreign material, especially by the ingestion of sand, may play a part. Acclimatization is also undoubtedly a factor in the tropics, it being a matter of common experience that new arrivals are especially subject to the disease, while "salted" individuals are relatively immune. Small children below the age of five are specially liable to bacillary dysentery, as are also those whose resistance has been lowered by any chronic and debilitating disease such as malaria, pellagra or tuberculosis.

**The spread of bacillary dysentery** —The spread of bacillary dysentery from man to man is due either to (1) direct or (2) indirect contagion.

1 Direct contagion takes place either by faecal contamination or from cooking utensils and food, and can only occur where the habits of the people are insanitary. It is undoubtedly a factor amongst primitive natives. In lunatic asylums direct contagion plays a prominent part and it has been pointed out that in these institutions the main focus of infection is the latrine.

It is probable that cases of endemic bacillary dysentery which were



noted in England during the 1914-18 War were due to direct infection contracted from returned soldiers who were convalescing from this disease. Such an instance was recorded by P. L. Sutherland in Wakefield, Yorkshire, in 1916.

2 Indirect contagion. Dysentery bacilli can be conveyed by the agency of house flies and possibly by water. The evidence against the house fly is fairly convincing. Working along the same lines as those pursued by Graham Smith in 1913 and 1914, the author (1912) originally obtained evidence that in Fiji house flies act as the main agents in conveying the infection by transferring it to foodstuffs. In the Pacific Islands house flies constitute a great plague in the dysentery season, and they are attracted by faecal material, especially dysenteric stools on which they feed readily. The bacillus can be conveyed to food by the fly in two ways: firstly by vomiting ingested dysenteric material directly on to the food—its normal prelude to feeding—and secondly, by defaecating on to any article of diet in the kitchen or on the table.

It has generally been noted that epidemics of house flies coincide very closely with those of bacillary dysentery, and that the incidence of the disease diminishes during the season when these insects are comparatively rare. This takes place, in the Middle East and in Africa, during the hot season when the majority of the larvae are destroyed by the rays of the sun. As originally pointed out by the author in 1912, it is possible by appropriate technique to isolate the dysentery bacillus, especially *Bact. shigae*, from the intestinal contents of house flies caught in association with dysentery patients and to demonstrate their presence in the intestinal tract of the insect for five days after ingestion.

S. T. Orton (1910) investigated an outbreak of 136 cases of dysentery in the Worcester State Hospital, U.S.A., and concluded that flies, which were present in great numbers, were responsible. A. Krontowski in 1913 found, in a series of carefully planned experiments, that dysentery bacilli could be isolated from the intestinal tract of flies for three days after ingestion. J. Smits (1915) in Sumatra, succeeded in isolating Shiga bacilli from flies caught in the neighbourhood of dysentery patients.

In 1919 the author repeated his original experiments with wild house flies caught in the Sinai Desert, and the same results were obtained with Shiga's bacillus while L. Dudgeon isolated Flexner's bacillus from similar insects. In 1918 this work was to a great extent repeated by J. F. Taylor in Salonica. He confirmed the main results, and found that the prospects of recovering the organisms diminished rapidly after twenty-four hours from the time of the original infection. He found also, as the author had already pointed out, that aberrant or mutant forms of dysentery bacilli were recovered after "passage" through the house fly. The mutations observed were so striking that this work should be repeated.

It has repeatedly been pointed out by other observers that there was some intimate association between house flies and dysentery, for instance, by W. E. Musgrave and A. G. Simon in 1914 in the Philippines, and by J. Morison and W. D. Keyworth (1916) in their study of flies in relation to epidemic diarrhoea and dysentery in Poona. J. Koch (1916) came to the same conclusion in his study of war dysentery in Germany, and N. Faichnie in his study of fly-borne disease in South Africa. H. Otto in the war epidemic in Poland in 1939 definitely associated bacillary dysentery with flies aided by direct contact amongst troops and hospital nurses. Reports from the Forces in the Middle East (1941) have amply confirmed the observations.

*General observations on the house fly*—Micro organisms are conveyed either externally or internally by the fly from the source of infection. Some organisms, mainly bacteria survive dryness only for a few hours while others spore producing varieties can survive for prolonged periods. As a means of transferring bacteria the body of the fly is most excellently adapted clothed as it is with hairs or setæ of varying lengths. Its legs which are brought frequently into contact with infected material closely resemble miniature brushes to which the organisms tenaciously adhere as a result the fly contaminates whatever substance it may subsequently visit within a certain time.

Most observers have concluded from their experiments that the possibility of flies becoming infected through the presence of pathogenic organisms in the breeding ground of the larvæ may be considered remote.

It has been shown experimentally that flies can carry and distribute *Bacillus typhosus* by infected feet, proboscides and excreta for several days and on several occasions this organism has been isolated from

'wild' flies caught in places where outbreaks were in progress. Under suitable conditions flies may act as carriers of typhoid mainly by infecting themselves with bacilli derived from mild unrecognized cases and carriers and the same is probably true for dysentery bacilli.

*Water and the spread of bacillary dysentery*—There appear to be adequate reasons for incriminating water as a factor in the spread of bacillary dysentery. In experiments made by the author in Fiji (1912) bacilli could be recovered after four weeks from sterilized water impregnated with *Shiga's bacillus* and after six weeks from tap water.

L. Dudgeon (1918) in Salonica concluded that *Shiga's bacillus* could be recovered from stored sterile water for a considerable period (576 hours in one experiment) and that the organism could live and multiply in stored water especially at low or medium temperatures, and it was found that, when so kept the bacillus retained its cultural and agglutinative characters. Apparently chlorination of water does not render it absolutely safe from infection for Dudgeon found that when chlorinated under expert guidance it was still capable of being infected with the *Shiga bacillus*. Dysentery bacilli are readily destroyed by direct action of the sun's rays and probably cannot survive long in

water which has been so heated. Despite this evidence, the author was unable to convince himself that, under modern war conditions, water played any great part in the dissemination of dysentery.

*The spread of bacillary dysentery by milk*—Various outbreaks of bacillary dysentery (Flexner) have been ascribed, more or less on insufficient evidence, to contaminated milk, but in Sonne dysentery this appears to have been definitely proved (G. K. Bowes 1939).

**Causal organisms** *History*—K. Shiga (1898) at Kitasato's suggestion identified the aetiological agent of acute dysentery by applying agglutination tests to bacteria he isolated from dysentery stools. This organism he obtained from 34 out of 36 cases and he subsequently inoculated himself subcutaneously with a killed culture of the bacillus, with the production of a severe local reaction. His original account was supplemented and augmented by others in 1901, 1902 and 1908. Two years later an almost identical discovery was made by W. Kruse (1900) of Bonn who found the same bacillus in dysentery cases in Laar Westphalia while S. Flexner, also in 1900 found in dysentery in the Philippine Islands a bacillus he thought at first was the same as that of Shiga. About the same time R. P. Strong and W. E. Musgrave found similar organisms in Manila. It remained for E. Martin and O. Leutz (1902) to demonstrate that the bacilli of Shiga and Kruse differed from those of Flexner and Strong in their serological as well as in their sugar reactions.

The toxins derived from the Shiga Kruse bacilli were investigated by C. Todd (1903, 1904) and an antidyenteric therapeutic serum was produced. In the meantime P. H. Hiss and F. F. Russell (1903) in North America had succeeded in isolating from cases of fatal diarrhoea in children an organism they called the Y bacillus which ferments mannite as well as dextrose. Since that time investigations of Kruse, Rittershaus, Kemp and Metz (1907) have led to the splitting up of the mannite fermenting group into a number of sub-groups and the matter was further complicated by still finer differentiations suggested by workers on this group during the 1914-15 War.

Modern bacteriologists recognize—

(1) The non-mannite fermenters of which the most important are Shiga's bacillus—*Bacterium shigae*—and Schmitz's bacillus—*Bacterium schmitzi*. In 1917 K. G. F. Schmitz described a bacillus closely resembling Shiga's bacillus but differing in production of indol from peptone and producing a distinct antigen.

(2) The mannite fermenting group now known as varieties of Flexner's bacillus which include a number of strains (formerly known as Strong's bacillus, Y bacillus, Newcastle bacillus etc.) for details see p. 560.

(3) The late lactose fermenting group represented by Sonne's bacillus—*Bacterium sonnei* which produces a distinctive clinical syndrome and which is becoming increasingly important.

Other bacilli have been described and accredited a role from time to time in the production of dysentery. Morgan's Bacillus No. 1 resembling *Bact. coli* has recently been discredited, so also has *Pseudomonas pyocyanea*.

(*B. pyocyaneus*), which is widely distributed in water sewage etc., and which may appear in numbers in the stools and on culture may inhibit the growth of the true dysentery bacilli.

**Dysentery bacteriophage**—During the last twenty years d Herelle has devoted considerable attention to the elaboration of dysentery cultures of a special bacteriophage. This dysentery phage is specific for both Shiga and Flexner groups and is apparently produced in the intestinal canal of patients recovering from bacillary dysentery. Great hopes were entertained that this discovery would result in a potent remedy and prophylactic but unfortunately these have not been realized. The whole subject of dysentery phage is discussed in d Herelle's work *The Bacteriophage and its Behaviour* (1926).

d Herelle observed that a filtrate of a convalescent dysentery stool had the power of clearing a broth culture of Shiga's bacillus. When a culture so dissolved was filtered and a few drops were added to a fresh culture the bacilli were dissolved and this could be repeated indefinitely. The Shiga bacillus, therefore, was the organism first recognized as being susceptible to bacteriophage. It is upon this organism also that most work has since been performed and it is the one upon which it is possible to isolate the most active races of bacteriophage for there exist strains of sufficient virulence to exterminate this bacillus even without enhancing their potency by passage.

**The nature of bacteriophage**—It is generally considered that bacteriophage consists of ultra microscopic particles having dimensions of 20-30  $\mu$  (millimicron). The size of the particles has been determined by testing the limits of its filtration through collodion membranes. It was thought by d Herelle to be a protobacterium either derived from the bacterium itself as an enzyme or a living autonomous thing which uses bacterial substances in order to reproduce. d Herelle described it as an autonomous living parasitic organism belonging to the group of filterable viruses which multiplies at the expense of bacteria and ultimately causes their destruction. moreover, there is an infinite number of bacteriophages.

It is very difficult to give an accurate account of the researches that are being carried out on this subject because different authorities vary so much in the presentation of their ideas. It appears that actually there are many races of bacteriophage which are virulent for Shiga's bacillus these races varying in the degree of their activity for other species of organism. The bacteriophage obtained from Flexner bacilli is apparently virulent only for members of that group.

Bacteriophage is isolated from the stools of patients convalescent from bacillary dysentery, from the stools of those affected with mild intestinal disturbances and also occasionally from the faeces of normal persons. In all cases there appear to be fluctuations in virulence of bacteriophage obtained from one individual case and also in the resistance of the bacteria and it appears that improvement in the patient's condition coincides with the moment when virulence of the bacteriophage excreted in the stools dominates resistance of the dysentery bacteria. Thus there are reproduced in the living body the same phenomena as in the test tube.

d Herelle has found in fatal cases of bacillary dysentery that at no time during the course of infection does the intestinal bacteriophage show any activity for Shiga's bacillus either for the stock strain or for those isolated from the stools of patients. From this it is argued that in an epidemic

simple cases of diarrhoea are in reality cases of aborted bacillary dysentery attributed to the rapidity with which intestinal bacteriophage adapts itself to pathogenic bacteria, hence healthy persons who are in immediate contact with dysenteric patients escape infection by rapid adaptation of the specific bacteriophage.

With a view to establishing a specific therapy, d Herelle himself ingested increasing quantities (from 1 to 30 c c) of bacteriophage suspensions aged from six days to one month without being able to detect the slightest inconvenience. As a result, prophylactic vaccination against bacillary dysentery by means of suspensions of anti dysentery bacteriophage was applicable to man but it is probable that any such prophylactic inoculation should be performed with a mixture of bacteriophage races anti Shiga anti Flexner, and so on.

D Herelle has quoted a series of cases of bacillary dysentery treated by the administration of specific bacteriophage this form of therapy being limited at first to cases in which the infection was proved by isolation of the pathogenic organism.

In the Instituto Oswaldo Cruz, Brazil a series of cases was treated with a virulent preparation of *B. dysenteriae* bacteriophage. It was concluded that possibly this method may best be combined with antiserum treatment, and in order to obtain favourable results the bacteriophage should be of maximum virulence.

**Bacillary dysentery in animals.**—Bacillary dysentery has rarely been proved to exist as a natural infection in domestic animals. H. Dold and W. Fischer (1916-20) found that the organism may be recognized in dysentery of dogs in China. It has been isolated by Ravaut and Dopter (1909) in Paris in monkeys in captivity and by H. H. Scott (1926) from a gorilla. Flexner bacilli have been found in these animals by W. Kruse (1912) and I. B. Bowman (1910) and there is some evidence that Sonne organisms are capable of producing a fatal disease in macaque monkeys.

**Reproduction of dysentery in laboratory animals.**—Shiga's bacillus is especially toxic for rabbits, horses and mice, but to a much lesser extent for guinea pigs. Sometimes after subcutaneous inoculation especially in rabbits the bacilli may become localized in the intestine and give rise to intense catarrh and necrotic lesions which often prove fatal (Vaillard and Dopter 1903). Unfortunately the intestinal lesions as a rule differ considerably from those usually seen in man. In rabbits, dogs and young pigs the infection becomes generalized and the organisms can be recovered from all the viscera. Possibly a fatal issue takes place too rapidly for dysenteric lesions of the bowel as seen in human subjects to develop fully. In laboratory animals subcutaneous inoculations produce intense inflammation at the site of injection accompanied by pyrexia. This is sometimes followed by paresis of the hind quarters and occasionally also by severe diarrhoea with blood and mucus.

**Reproduction of the disease in man.**—In 1900 R. P. Strong and W. E. Musgrave reproduced bacillary dysentery in a condemned criminal by administering by the mouth a 49 hour culture of Flexner's bacillus. The man recovered after a typical attack of bacillary dysentery and the organism was recovered from his stools.

There are three authentic cases of accidental laboratory infection of bacillary dysentery in man. W. Kruse (1901) mentions a doctor in his laboratory at Bonn who infected himself with cultures of Shiga's bacillus and there after suffered from a mild attack. S. Flexner (1900) in Baltimore described the case of one of his assistants who accidentally aspirated a culture by the mouth and forty eight hours after suffered from diarrhoea and tenesmus with passage of blood and mucus. A laboratory contracted infection is also reported by L. S. Lippincott (1925) when an assistant sucked up by mistake an emulsion of a freshly isolated culture of Flexner bacilli. Six days later clinical dysentery developed and the same bacillus was isolated from the stools.

**Carriers of bacillary dysentery**—These may be classified as healthy, convalescent relapsing and chronic carriers.

The *healthy carrier* is one who excretes dysentery bacilli in a normal healthy motion without having suffered from an acute attack of the disease. This must be rare and we agree with Macalister that this group is not important for since the cases reported by Kruse, Conrad and Mayer many years ago little work has appeared except that by A. Vazquez Colet in the Philippines in 1925. The bacilli may however appear in the faeces intermittently as is shown by I. Verzar and O. Weszechzy (1916). Amongst 417 cases of convalescent dysentery (War cases in Germany) they discovered 77 carriers of whom 70 were excreting Flexner's bacillus. K. Saisawa and B. Tanabe (1926) examined 2,847 recruits in the Japanese Army and found that 0.52 per cent were healthy carriers; among soldiers in barracks out of 4,648 examined 0.32 per cent proved to be the same. Among the total of 33 carriers Shiga's bacillus was found in one case Flexner's in 10 and the *S. flexneri* bacillus in 17.

The majority of bacillary dysentery carriers are *convalescent carriers* i.e. persons who, after an attack of bacillary dysentery continue to pass viable bacilli in the faeces usually together with blood and mucus. Saquépée considers that the *formes frustes* the slight and clinically almost unrecognizable forms of the disease play an important part in its spread.

Friedmann in 1913 reported an epidemic in which eighty six men in a cavalry regiment were attacked and which was eventually traced to a convalescent carrier and in 1921 Keersmakers described an extensive epidemic amongst the Brussels garrison which was traced to a prisoner of war who had recently returned from Germany.

J. A. Arkwright, W. Yorke, O. H. Priestley and W. Gilmore found that two out of fifty convalescent dysentery patients were excreting Shiga's bacillus six months after the attack. A. M. Kennedy and D. D. Rosewarne found only six carriers of which three were Shiga and Flexner in 5,000 faeces examinations. Similarly J. O. Barratt (1916) in a minute examination of fifty convalescent dysenteries from Gallipoli and Egypt found only three carriers.

The *relapsing carrier* may be defined as one by whom dysentery bacilli are passed in the faeces owing to renewed activity of the organisms.

in the intestinal canal. N. P. Hudson has reported upon such a case. The patient contracted Flexner dysentery in June, 1918, and during a relapse three and a half years later, in January, 1922, the bacillus was again isolated. The author has had a similar experience: an officer contracted Shiga dysentery in April, 1917, the bacillus being isolated on culture; exactly three years later he suffered from a clinical relapse in England, during which the same organism was isolated.

The *chronic carrier* may be defined as one who is incompletely cured of the disease in a clinical sense, and continues to pass dysentery bacilli in the faeces. The importance of this factor was amply confirmed in the 1941 Libyan campaign.

W. Fletcher (1917), working in England on War convalescents, found only one carrier of Shiga bacillus among 800 men; on the other hand, dysentery bacilli of the Flexner type were isolated in 2.25 per cent. Again W. Fletcher and D. L. Mackinnon in 1918 found that Shiga carriers were rare in a group of 935 war convalescents—1.39 per cent—while 61 were Flexner carriers. E. Berent and L. Nègre found 18 chronic carriers among a group of 67 pilgrims who had recently returned from Mecca.

The infective bacilli emanate from the diseased mucosa. According to W. Fletcher the hiding place of the organisms in the intestinal mucosa from which dysentery bacilli can be obtained are—

- (a) Retention cysts in the submucosa originally described by the author (Fig. 8)
- (b) Collections of pus which form beneath the pigmented scars of healed ulcers
- (c) Undermined margins of chronic ulcers

The carrier state in bacillary dysentery does not, as a rule, persist for any great length of time. H. M. Perry (1925) paid especial attention to this point in the case of Shiga carriers. He showed that the state usually persisted from four to six months, and at the end of a year only 4 per cent were still carrying dysentery. In the case of Flexner infections it was higher, 7 per cent. The carrier state may last at most three or four years. For instance, Hudson reported a case of Flexner infection in which the bacillus could be demonstrated for three and a half years.

The great majority of carriers, even when apparently healthy, are still suffering from ulceration of the intestinal mucosa, wherever sigmoidoscopy has been carefully performed, as in the series investigated by K. Saito and B. Tanabe (1926), ulceration or inflammation of the lower sigmoid or of the rectal ampulla has been revealed.

According to A. Vazquez Colet (1925) the serum of the carrier agglutinates the homologous organisms and emulsions made from stock cultures give the best result. Treatment of the carrier state by autogenous vaccines in order to rid the intestinal tract of these organisms

has proved of little avail (W. Fletcher, 1917). Recently sulphaguanidine treatment has proved valuable.

The detection of carrier cases corresponds with the annual seasonal outbreaks of bacillary dysentery in the Philippines and appears to run parallel with the number of clinical cases.

**Dysenteric toxins.**—In 1903 H. Conrad produced an autolysate of Shiga's bacillus which was toxic for rabbits and guinea pigs. After incubation, an 18 hours old culture was suspended in saline and further incubated for 24–48 hours at 37° C. when centrifuged, the yellowish supernatant fluid was diluted with five times its volume of saline and filtered through a Berkefeld candle. This product, injected sub

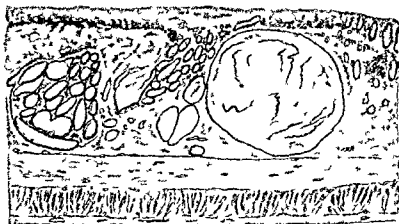


Fig. 8—Chronic bacillary dysentery (Shiga infection) microscopic section showing formation of submucous retention cysts from adenomatous extensions of Lieberkuhn follicles

cutaneously into guinea pigs in a dose of 0.1 cc. proved fatal in 48 hours. In rabbits death was preceded by diarrhoea, collapse, and paralysis of the extremities. Neisser and Shiga further noted that these toxic substances were precipitated by alcohol and ether and destroyed by heat at 75° C., while C. Todd (1904) prepared a soluble toxin which was highly active in rabbits and horses, but much less so in guinea pigs, rats, and mice. Dopfer (1905) described definite lesions in the spinal cord, chiefly chromatolysis of the anterior horn cells, and these were noted as frequently after injection of toxin as after the bacilli themselves.

R. Kraus and R. Dorr (1905) concluded that Shiga's bacillus gives rise to two toxins, one a soluble exotoxin fatal to rabbits and guinea-pigs and giving rise to a specific neutralizing antitoxin, the other an insoluble endotoxin present in bacterial bodies. Later Bessau (1911) concluded that there are two toxins, one, parietic or neurotoxin causing



paralysis of the muscles the other, intestinal toxin causing diarrhoea and chronic marasmus

The dysenteric toxins are very resistant to heat and to the action of light and ferments, their activity is neutralized when they are emulsified with fresh mucous membrane, especially that of the rabbit's intestines

W W C Topley and G S Wilson (1939), in summarizing our present knowledge of this subject, consider that Shiga's bacillus gives rise to a soluble toxin, whilst Flexner bacilli do not. The toxins of Shiga's bacillus are much more potent than those of the Flexner group, some strains of the latter having actually been proved to be completely a toxin

As regards the nature of the toxin, it is believed to be intermediate in position between an exo- and an endotoxin, possessing some of the properties of each. In order to prove that the dysentery endotoxin is distinct from the exotoxin, it would be necessary to show that an anti-exotoxin serum has no neutralizing effect upon the endotoxin, but it has been found that such a serum will neutralize Shiga toxin whichever way it is prepared

K Schroer (1940) has studied the toxins of Schmitz's bacillus. The exotoxin was obtained from a filtrate of broth cultures by precipitation with trichloroacetic acid, and the endotoxin from young cultures grown on agar. The endotoxin is rather weaker than that of Shiga's bacillus. Rabbits are most sensitive to exotoxin, guinea-pigs to endotoxin. The conclusion is reached that, in production of toxins Schmitz's bacillus occupies a position between active *B. shiga* and inactive *B. flexneri*.

C C Okell and A V Blake (1930) produced a modified toxin toxoid. This is prepared from the filtrate toxin by the addition of 0.6 per cent formaldehyde so that after three weeks at 37° C the original toxin becomes innocuous. A horse immunized with toxoid however, yielded a very potent antidysentery serum after six weeks treatment.

**Habitat of the dysentery bacillus in the human body—**The dysentery bacillus is an inhabitant of the intestinal canal and, in the great majority of cases, solely of that tract. It is found mostly in the mucous membrane of the lower part of the small, and through the whole extent of the large intestine. The organisms occur in the lower part of the mucous membrane in immediate contact with the muscularis mucosae coat, rarely penetrating beneath it. It is, therefore, from this layer that the dysenteric toxins are absorbed and carried into the blood stream. There is some evidence too, that in the large intestine the solitary lymphoid follicles are first infected. In early cases of the disease dysentery bacilli can be isolated with comparative ease from the inflamed mucous membrane, and occasionally at autopsy from inflamed mesenteric glands.

Dysentery bacilli have rarely been found in the blood, gall-



1 h Dr G Mather Cord ner

Barium enema of chronic bacillary dysentery  
(Flexner infection) showing smooth outline  
of bowel patches in descending colon and  
normal outline of the cæcum

**CHRONIC BACILLARY DYSENTERY**

**PLATE I**



2

3

1, Acute bacillary dysentery necrosis 2, Diphtheroid membrane in bacillary dysentery 3, Subacute bacillary dysentery



4



5

4, Chronic bacillary dysentery 5, Mixed infection of amœbic and bacillary dysentery, A—amœbic ulcers, B—bacillary necrosis of mucosa

## PATHOLOGY OF THE COLON IN BACILLARY DYSENTERY

(Drawn by P H Manson Bahr after W Fletches and M W Jepps)

PLATE II

bladder urine and spleen L Roenthal (1903) isolated Shiga's bacillus in pure culture from the spleen and from the heart's blood in a man of twenty years of age who had ulceration of the large intestine H T S Aveline A E Bycott and W F Macdonald obtained Flexner's bacillus from the spleen in 1908 S T Darling and I B Bates (1912) recorded the isolation of Shiga's bacillus from the blood of a negro who died four days afterwards from dysentery which was verified post mortem and F Fraenkel (1915) succeeded in isolating the Flexner's bacillus on bile-medium culture once out of 950 attempts J C G Iedingham and W J Penfold (1915) recorded the isolation of Shiga's bacillus from the blood of a patient originally suffering from paratyphoid A A Ghon and B Roman (1915) recovered the Flexner's bacillus from the blood and spleen in Germany and L Dudgeon in 1919 in Salonica succeeded in obtaining it from the blood twice out of 145 attempts P C Flu (1918) in Java obtained Flexner's by blood culture in a child aged four years suffering from typhoid symptoms C M A Maer (1918) obtained a profuse growth of Shiga's bacillus by blood culture in a fulminating case of bacillary dysentery with cerebral symptoms the bacillus being also isolated post mortem H Spranger (1926) in Germany by using a special bile medium succeeded in isolating Shiga's bacillus twice Flexner's bacillus once and the Y bacillus once by blood culture

The dysentery bacillus has very occasionally been grown from the bile at post mortem for example by A Ghon and B Roman (1915) in Germany and by A Connal and E C Smith (1925) in Nigeria P C Flu in 1918 found that bile does not definitely inhibit growth of dysentery bacilli and he was able to isolate the organism from it two months after the last intravenous injection of Flexner bacilli into rabbits C W Duval and Bassett (1908) recorded isolation of Shiga's bacillus from the liver

Records of isolation of the dysentery bacillus from urine are scanty S R Bruenauer (1916) obtained dysentery bacilli in four out of fifty four bacteriologically proven cases A Ghon and B Roman succeeded in doing so once in a male and E Fraenkel (1915) found bacillus Flexner's once out of thirty six cases of mild dysentery Dysentery bacilli may therefore be present in the urine during the acute stage of the disease or in early convalescence

On one occasion R R Ellworthy (1918) isolated Shiga's bacillus from the synovial fluid in dysenteric arthritis He employed a large amount of joint exudate for the purpose and as a result four colonies of Shiga's bacillus appeared

**Geographical distribution and epidemiology**—Bacillary dysentery is a widespread disease and although at the present day more frequent in the tropics and sub tropics where the sanitation is either primitive or non-existent it still occurs from time to time in epidemic form in highly cultured northern European countries Dysentery was rife in mediæval England at a time when filth squalor and

overcrowding were only comparable with primitive tropical conditions at the present day. In recent years epidemics have been recorded in France, Germany, Great Britain, and the United States. In civilized countries the disease especially affects small children, in whom it may cause a considerable mortality. In these countries too, it is endemic in lunatic asylums and similar institutions. In France, Italy, and Germany bacillary dysentery is apt to attack soldiers in barracks and in encampments. There was for instance, the well known epidemic among the Prussian Guard at Döberitz in 1901 (Drigalski). In Russia under the Soviet regime widespread and extensive epidemics have been recorded. That bacillary dysentery is by no means necessarily associated with high atmospheric temperatures is shown by the fact that outbreaks resembling this disease have been recorded in sub arctic countries.\*

Bacillary dysentery has always been associated with the armies in the field. It apparently decimated the armies of Napoleon on the retreat from Moscow, it was present in the Crimean War, it was the chief form of dysentery in the South African War of 1900-02 (88,108 cases with 1,842 deaths), and it was undoubtedly a feature of the Franco Prussian War of 1871, leading to epidemics in Germany which lasted for several years. In the 1914-18 War it furnished a considerable proportion of the casualties on all fronts, especially in Gallipoli, Salonica, Egypt, Palestine, Mesopotamia, and East Africa, while even in France and Flanders it assumed considerable dimensions in 1917 and 1918. In the former year it accounted for 8.76 per thousand of casualties in France and no less than 486 per thousand in East Africa, while in Gallipoli, in August, 1915, it was responsible for a high proportion of the 120,000 medical casualties evacuated from the Peninsula within three months†. To quote Shiga, it is always a constant companion of war, and it has been more fatal to armies than powder or shot."

In India, Malaya, and the Pacific Islands, bacillary dysentery is responsible for widespread and particularly fatal epidemics. In the Fiji Islands, for instance, epidemics in 1884 caused a mortality rate of over 130 per thousand and even in recent years it has varied from 52 to 128 per thousand.

Wherever it occurs, bacillary dysentery is likely to appear in epidemic form and these epidemics are usually subject to seasonal variations, in the tropics, where there is a well marked wet season, the disease tends to appear at the end of the rains. In India, also, where bacillary dysentery epidemics are of annual occurrence, L. Rogers (1913) has shown that a characteristic seasonal incidence occurs. During the colder months of January and February bacillary dysentery almost disappears, to rise with the advent of the warmer weather; but in

\* The dysentery so frequently referred to in the narrative of Scott's and Shackleton's Antarctic explorations seems to have been an irritative enteritis due to a too rapid return to a meat dietary after partial starvation.

† It was pointed out by J. C. G. Ledingham and L. C. M. Wemyss, and also by the author that the majority of the dysentery cases in the epidemics in Gallipoli and Mesopotamia during 1915 and 1916 were bacillary in origin and only some 15-20 per cent. were amoebic.

the very hot May and June there is a fall. The maximum increase follows closely on the monsoon rains in July, reaching its peak in August and September.

Balfour Kirk has summarized the epidemiology of bacillary dysentery in the tropics as follows —

- (a) Rains deter occupants from defæcating at a safe distance from their villages
- (b) Waterlogging of the soil prevents bacilli from dying out
- (c) The people are more liable to chills which precipitate an acute or subacute attack
- (d) Natives crowd together thus increasing the chances of infection
- (e) There is an increased risk of pollution of water supplies

In Arabia very virulent epidemics of bacillary dysentery are frequent among Mohammedans on their annual pilgrimage to Mecca. The high mortality rate and the infectious nature of the disease among them may be appreciated from the studies of M. A. Ruffer and J. G. Willmore at the Pilgrim Station of El Tor in Sinai in 1909 and 1910. The classical types of *B. shiga* and *B. flexneri* were isolated, but the commonest was a subspecies of the latter named El Tor No. 1, from which these workers prepared a therapeutic antiserum.

#### BACILLARY DYSENTERY IN ITS RELATION TO INTESTINAL AMOEBIASIS

It is probable that no proper conception can be obtained of the true distribution of bacillary dysentery from isolated published statistics or from official sources. There are two main factors to account for discrepancies which will be found in this particular section —

1. The bacillary disease can only be diagnosed with scientific certitude by isolation of the dysentery bacillus, and this is a procedure demanding skill, a properly equipped laboratory, an experienced scientific director, and the provision of adequately trained laboratory assistants. Such facilities are not to be found everywhere in British Crown Colonies and in the more undeveloped portions of Central Africa and Central America.

2. The recognition of amoebic dysentery and the differentiation of *Entamoeba histolytica* from the non-pathogenic amoebæ require the attention of a properly trained protozoologist. The number of specially trained personnel is limited, and many are the pitfalls which beset the tyro in the identification of the true dysentery amoeba in all its various stages. There exists, therefore, a not unnatural tendency among inexperienced practitioners to "rush in where angels fear to tread," and too readily to diagnose amoebiasis in tropical countries, where this infection is naturally prevalent, and where the disease evokes more popular attention than in northern climes.

There is at present no uniformity in the matter of diagnosis nor general agreement on the basis by which these diagnoses are made, and until there is some universal and generally accepted standard, discrepancies and paradoxical statements are bound to be noted and

sudden *boulercements* of statistics to occur from time to time. We cannot always sincerely believe that the nature of the prevailing form of dysentery has changed with this almost startling rapidity. The truth is that bacterial infections, in all their different and perplexing phases, are much more intricate and difficult to detect than are protozoal.

For more detailed information regarding the world incidence of the two main forms of dysentery, the reader is referred to Table X, pp 136-150.

## CHAPTER VII

### THE BACILLARY DYSENTERIES (*continued*): PATHOLOGY, SYMPTOMATOLOGY AND COMPLICATIONS

**Mild cases.**—It is difficult to describe the pathological appearances of mild bacillary dysentery because since patients do not succumb to mild infections opportunities for post mortem examination are infrequent. The earliest lesions noticed by the author appear to originate in lymphoid follicles of the large intestine. These give rise to superficial snail track ulcers which travel across the bowel spreading on the free edges of the transverse folds of the mucosa together with this there is catarrhal inflammation of the mucous membrane with the secretion of viscid mucus.

**Very acute cases.**—The fully developed pathological picture appears to consist of acute hyperæmia of the large intestine which eventually results in a gangrenous process (coagulation necrosis) of the mucous membrane. This is seen especially in the lower portions of the large intestine, but may affect the last eight feet of the ileum and very exceptionally, the whole small intestine (of which the author has investigated one case). This process is especially severe in the rectum and pelvic colon, but the cæcum, hepatic and splenic flexures appear to be particularly selected. Acute inflammation and necrosis are brought about by direct action of dysenteric toxin on the mucous membrane, possibly also by its elimination from the blood stream. In especially virulent cases death may take place in as short a time as fifty six hours from the onset.

**Stage of hyperæmia.**—At autopsy the appearance of the cadaver suggests intense toxæmia, but there is no wasting. There is paralytic distension of the large intestine, the mucosa is found to be bright scarlet red, very friable, dripping with blood, but there is no infiltration of the walls of the viscus. The lumen of the bowels is filled with viscid mucus intermingled with blood, in the small intestine there is a similar outpouring, tinged green with bile. Abundant signs of widespread toxic absorption are usually found. Thus, a general lymphoid peritonitis is present, with exudation of free serous fluid into the peritoneal cavity lymphoid foci of the peritoneal surface, and œdema of the mesentery. The mesenteric glands are enlarged, red,



and softened. Very commonly post mortem intussusception of the small intestine is present. There is engorgement of the right side of the heart, the liver and kidneys enlarged and congested show parenchymatous degeneration (toxic nephrosis), the gall bladder contains scanty, tenacious amber coloured bile, the spleen is dark red and slightly disfluent. the suprarenal glands may show central necrosis.

In less acute cases which do not run such a rapid course, the mucous membrane has a rosy plum colour, mottled with numerous submucous hæmorrhages while the whole bowel is oedematous and consequently much thicker than normal (Plate IV, 1, facing p 66). The numerous extravasations of blood into the submucosa constitute the acute hæmorrhagic type. H. R. Daw and N. H. Fairley (1921) describing the pathology of a series of 259 acute and fatal cases noted together with the acute changes in the intestines, toxic spoiling of the viscera. In one instance Flexner's bacillus was obtained from a splenic abscess. Myocarditis and pericarditis were common.

*Stage of necrosis* — In those who survive this process for more than a week the stage of coagulation necrosis is reached. Then the cadaver shows very considerable signs of wasting. The large intestine, especially the sigmoid flexure is spastic and narrowed. The bowel wall is thickened by oedema, hæmorrhages and cellular infiltration. The appendices (epiploica) are engorged discoloured even oedematous. The defunct mucous membrane is converted into an olive green brownish, or even blackish substance which is rigid to the touch and pitted on the surface like a lava field (Plate III 2 facing p 50). The last few feet of the ileum may be similarly affected. This greenish material represents the diseased mucous membrane extending down to the muscularis mucosæ. This colour is mainly due to staining of the dead tissue by bile and partly to the altered blood pigments. The intestinal contents consist of dark greyish fluid containing altered blood but owing to destruction of mucous cells show little mucus. The necrotic mucous membrane can be scraped off with difficulty, revealing numerous small hæmorrhages. Occasionally patches of necrosis are found scattered throughout the length of the large intestine, interspersed with areas of comparatively normal mucous membrane.

Apparently Nature's cure of this destructive process consists in exfoliation as in a diphtheritic membrane, exposing a raw granulating surface. It is probable that a bowel thus destroyed cannot possibly recover and even if this were possible occlusion of the lumen would result. In this type of dysentery death usually takes place at the end of the third week. By this time the body is emaciated, the subcutaneous fat has completely disappeared, the omentum is denuded of its fat, the abdominal viscera are wasted and the mesenteric glands hard and fibrous. Where the necrotic process affects only limited portions of the bowel, ulcers of an irregular outline tend to form. Usually they are oval or irregular and communicate with each

other by submucous burrows or sinuses. This riddled appearance involves the whole of the large bowel (Plate II, 1-4)

P Remlinger and J Dumas (1915) describe an acute suprarenal syndrome in 4 per cent of bacillary dysentery cases. The diagnosis is verified at autopsy by finding the adrenal hypertrophied. The syndrome appears in benign as well as in severe cases, and at any period of the disease. Histologically, in the suprarenals there is congestion of the capillaries and diffuse coagulation necrosis affecting both the cytoplasm and the nuclei of cells. In view of this pathology, injections of eucortone are indicated in treatment. The resemblance of the clinical state to Simmonds disease has been noted.

*The stage of recovery*—When the mucous membrane has been as completely destroyed as in the description already given, it is difficult to visualize how it can be restored to its normal condition. Observations indicate that regeneration of the mucous membrane takes place from islands of mucosa which have escaped destruction. Repair appears to consist of proliferation of the columnar epithelium and the laying down of fibrous tissue, the healing mucosa being represented by a granular surface interspersed with fibrous scars. Where this has failed, the surface is covered with bleeding granulation tissue extending throughout the whole length of the large intestine or in scattered patches, especially in the lower portion. Over production of granulomata may result in pseudo polyposis. The transverse colon is sometimes distended and sacculated. Often coils of the large and small intestine may become matted together by plastic peritonitis. Pericolic thickening and general hyperplasia of the large bowel as observed in chronic amœbiasis do not follow.

**Pathology of chronic bacillary dysentery.**—Chronic ulceration of the large bowel is the outstanding feature in chronic bacillary dysentery. The lesions are at first small, lenticular ulcerations of the mucous surface involving the mucosa, sometimes they are found in the lower ileum (Plate II, 4)

The more advanced chronic lesions have been observed in pensioners from the 1914-18 War, and are common enough in natives, who suffer frequently from recurring attacks of longstanding bacillary dysentery. These lesions consist of irregular ulcerations of the mucosa which rarely penetrate beneath the muscularis layer. In a certain proportion of Europeans who have contracted chronic dysentery the main lesions appear as a granulomatous mucous membrane without demonstrable ulceration. In bacillary dysentery the ulcers are irregular in shape and run at right angles to the long axis of the bowel, the edges are not undermined and the base consists of greyish or brownish slough. In the chronic form pseudo polypoid granulomata are sometimes so extensive as to occlude the lumen. Further features are given in the accompanying comparison.

*Chronic Bacillary Ulceration*

Ulcers commence on free edge of transverse folds and run at right angles to the long axis of the gut. Ulcers are serpiginous with ragged edges, they often communicate with neighbouring ulcers and as a rule involve the muscularis mucosa.

*Amoebic Ulceration*

Ulcers commence as small abscesses in the submucosa which on rupturing, ulcerate and are distributed parallel to the long axis of the gut. Ulcers are oval, regular with undermined edges, rounded or heaped up margins, discrete, flask shaped on section, involving mucous membrane submucosa and muscular coats. They originate in the submucosa.

Perforation of the bowel as a result of bacillary dysentery may take place, although it is very rare compared with chronic amoebiasis. The author recorded (1919), in a series of over 300 autopsies in Egypt three instances of ante mortem perforation of the transverse colon with general peritonitis.

*Retention cysts*—The author described a curious pathological condition which is the direct sequel of chronic bacillary dysentery and which is frequently seen in autopsies on Eastern natives—the formation of tapioca like mucous retention cysts varying in size from that of a hemp seed to that of a cherry, which are distributed unequally through the large intestines causing excrescences on the peritoneal surface, on incision clear, jelly like mucus can be expressed. The retained material is often infected with Flexner bacilli and with *B. coli*, and may ultimately result in abscesses within the bowel wall. These cysts form from proliferation of the mucous membrane beneath the muscularis and explain the intractable mucous colitis which is so frequently a sequel and which is so difficult to treat. W. Fletcher and M. W. Jepps (1924) in their studies on dysentery in the Federated Malay States describe this condition as quite common in chronic cases and in carriers. Repair of chronic ulceration takes place extremely slowly by the formation of pigmented scars which are visible as bluish depressions, beneath which lie retention cysts (Fig 8 p 41).

**Mixed infections**—The frequency with which tuberculous ulcerations and hyperplastic tuberculosis of the large intestine are noted in natives of the tropics who have suffered previously from bacillary dysentery makes it probable that the damaged mucous membrane offers lowered resistance to tubercular infection.

*Amoebic* ulceration may co exist with bacillary disease. Typical lesions are superimposed on a fibrotic and scarred bacillary bowel and, *per contra* the author has seen acute bacillary dysentery grafted on amoebic ulceration, but these cases are by no means frequent (Plate II, 5).

Chronic bacillary dysentery may, also, be the starting point of a fatal generalized *B. coli* pyæmia, and the author, in association with



1



2

1, Amœbic Dysentery Typical patches of infiltration and ulceration of ascending colon, showing "Dyak hair" sloughs 2 Bacillary Dysentery (Shiga infection) Coagulation necrosis of lower portion of ileum, showing characteristic green coloration of the destroyed mucous membrane

# INTESTINAL LESIONS IN AMŒBIC AND BACILLARY DYSENTERY (Half nat size)

PLATE III

J I Enright, has described a *B coli* nephritis in which pyemic abscesses form in the Malpighian bodies and finally lead to large suppurating abscesses. It is therefore possible that ulceration of the large intestine may be primarily responsible for those chronic *B coli* infections so commonly encountered in tropical practice.

*B coli* infections —J I Enright and the author in 1917, in Cairo described amongst Turkish and Arab prisoners of war a pyemia in which the kidneys were specially affected caused by *B coli communis* or allied organisms. Nine cases were diagnosed during life and six postmortem. Chronic bacillary ulceration of the large intestine and rectum were common and it was demonstrated that the organisms gained entrance to the blood stream through the lesions in the intestinal mucosa and were present in the blood and urine. The infection was found particularly in association with chronic bacillary dysentery and parenchymatous degeneration of heart liver spleen and kidneys was evident. In smears from the organs the colon bacilli showed marked polar staining. The bacilli isolated in pure culture from abscesses in the cortex of the kidneys were divided into nine groups by their sugar reactions. Three failed to ferment lactose and a type corresponding to *B neapolitanus* Emmerich was most frequently encountered.

*Protozoa and their cysts in bacillary dysentery exudates* —The existence of mixed infections of amoebic and bacillary dysentery may cause confusion to pathologists and clinicians. That such infections do exist there can be no reasonable doubt. On two occasions the author found active *Entamoeba histolytica* in a stool with a characteristic bacillary dysentery exudate from which he was able to isolate Shiga's bacillus but he has never seen cysts of *E histolytica* in a bacillary dysentery stool. Other intestinal protozoa are encountered. Sometimes the vegetative form of *E coli* may appear and these have to be differentiated from similar stages of *E histolytica*. The reader is referred to the Appendix, p 533, for details on this point. During the stages of recovery intestinal flagellates such as *Chlamydomonas*, *Trichomonas* and even *Giardia* may be present in considerable numbers. It is probable that these organisms find in the bacillary dysentery stool a medium which is congenial for their propagation and it is probable, too, that their presence increases inflammation and irritation.

Double infections of the amoeba (*E histolytica*) and the dysentery bacillus are not so common in Europeans as in debilitated, half starved and exhausted natives. Some excellent pathological specimens illustrating this point were collected by H R Dew in Egypt during the Great War and were in the collection of the Royal College of Surgeons. W Fletcher and M W Jepps (1924) record that in complicated cases no other bacillus was found so frequently in amoebic dysentery as *B dysenteriae*, which was isolated from 27 out of 198 cases, also that in a number of fatal cases of chronic dysentery they found lung lesions due to *B mucosus capsulatus*.

*Relationship of the pathological lesions to the presence of the dysentery bacillus* —During the World War (1919) the author showed that the

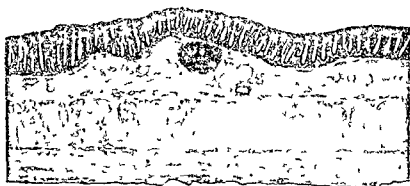
dysentery bacillus could be isolated in the early stages directly from the mucous membrane, but when necrosis had taken place this organism could be recovered from the deeper layers of the bowel.

In the necrotic stage it is necessary to scrape away the dead tissue, while in chronic dysenteric ulceration the organisms (*B. shigae*) can be recovered from the bases of the ulcers. It was found that in 55 cases of the chronic form the large intestine was affected as follows —

	Cases
Whole of the large intestine	24
Caecum and transverse colon	1
Rectum sigmoid and transverse colon	3
Rectum, pelvic colon and sigmoid	17
Sigmoid alone	5
Rectum alone	5

The tendency is for chronic bacillary ulceration to occur mostly in the lower part of the intestine, i.e. in the sigmoid colon and rectum. In the upper portions ulcers are generally shallow and increase in depth and extent towards the lower portion. In two cases chronic bacillary ulcers were present in the lower part of the ileum and the dysentery bacillus (*B. flexneri*) was isolated.

**Histopathology** —The histology of the bowel in bacillary dysentery is a subject to which the author has given special attention and can best



P. H. M. B.

Fig. 9 —Section of colon in acute bacillary dysentery (*Shiga's bacillus*), showing inflammatory reaction especially in the solitary lymph follicle.

be illustrated by means of diagrams (Figs 9-10). In the acute stages the mucous membrane is invaded by inflammatory cells mostly of the plasma type. The capillaries are engorged and there are numerous small haemorrhages, the goblet cells being enlarged. In the submucosa there is engorgement of the veins with considerable accumulations of inflammatory cells. The inflammatory changes are most intense in the vicinity of the lymphoid follicles.

In the necrotic stage the crypts of Lieberkühn's follicles are mostly destroyed, so that no definite structure can be distinguished. This layer has undergone coagulation-necrosis and is converted into a structure in which small hæmorrhages, accumulations of leucocytes



P. H. M. B.

Fig. 10.—Microscopical section of the large intestine in bacillary dysentery. Showing necrosis of the mucosa, cellular infiltration, and hæmorrhages into the submucosa.

and pyknotic nuclei are visible. The muscular fibres of the muscularis usually escape. The submucosa is thickened to two or three times its normal width, distended with inflammatory exudate and the seat of numerous hæmorrhages. Chief features are thrombosis and the destruction of the blood-vessels, especially the veins. In the capillaries, it is

possible to recognize macrophage endothelial cells (histiocytes) apparently derived from the capillary endothelium. They are often large, 15-20  $\mu$  in diameter, and contain ingested red cells, sometimes leucocytes. When they appear in the stools they are apt to give rise to confusion as they bear a close resemblance to amœbæ (Fig 11). In these severe cases the muscular fibres of the circular and longitudinal muscular coats have undergone toxic spoiling. Cases have been seen in which all layers of the bowel wall have undergone coagulation necrosis.

Exfoliation of the necrotic mucosa is followed by granulation tissue, and the submucosa becomes the seat of newly formed capillary vessels.

In the stage of repair, proliferation of the columnar epithelium takes place from the fundi of Lieberkühn follicles. The submucosa remains thickened and becomes the seat of fibrotic changes.

*Chronic ulceration*—The formation of a chronic bacillary ulcer is illustrated in Fig 12. Ulceration proceeds from the fundi of the destroyed follicles while fibrous tissue forms in the immediate vicinity. The formation of mucous retention cysts proceeds from the base of the Lieberkühn follicles forming cystic pseudo adenomata distended with mucoid secretion. At first they are lined by columnar epithelium, but later the cells are destroyed and the cavity is lined by basement membrane (Fig 8, p 41).

### SYMPTOMATOLOGY OF BACILLARY DYSENTERY

The practitioner in the tropics soon realizes that it is only in the acute and obviously toxic cases that his clinical acumen will permit a definite and positive diagnosis of bacillary dysentery. Even with the assistance of an efficient laboratory service he must still be guided by clinical sense. When several cases of an acute dysentery of sudden onset with prostration and toxæmia occur in the same neighbourhood and especially when children and the enfeebled are attacked, then a diagnosis of bacillary dysentery may with certainty be made, but it is all important that, in every case, this surmise should have reliable laboratory confirmation. Sporadic cases, and especially those not uncommon instances of relapsing bacillary dysentery may be difficult to differentiate from amœbiasis. It seems superfluous to labour the point that this question of diagnosis is all important and that there is no disease in which the co-operation of the clinician and the pathologist is so essential.

In clinical cases of bacillary dysentery, it can be stated at the outset, all degrees of severity occur from a mild apparently harmless diarrhœa to a toxic fulminating choleraic disease which may be fatal within two or three days from the onset. Divergence in clinical types are noted in adults in children in natives in Europeans, in different epidemics, and in different countries. It is a matter of importance that severe cases should be recognized early and the appropriate steps taken.



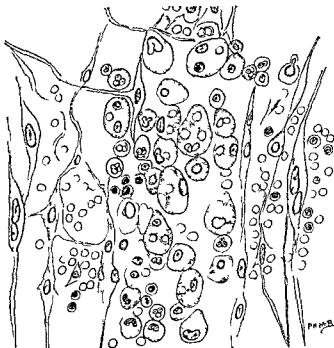


Fig. 11 —Derivation of macrophage cells from the endothelium of capillary vessels of the submucosa in acute bacillary dysentery (*Shiga's bacillus*)  
Many of the cells have ingested red blood corpuscles ( $\times 500$ )

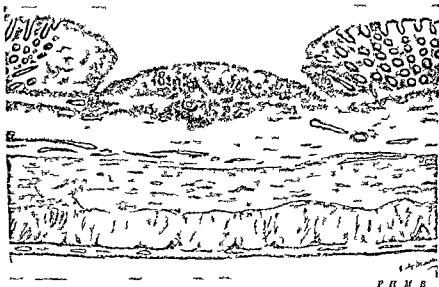


Fig. 12 —Microscopic section of chronic bacillary dysentery ulcer (*Flexner's bacillus*)  
in the large intestine showing structure

otherwise irreparable damage to the mucous membrane may take place, moreover, the sooner the patient comes under treatment the less likelihood there is of the disease becoming chronic and intractable.

Though there is no golden rule, the following symptoms may be regarded as cardinal: intermittent or remittent fever, great abdominal pain, tenesmus, and excessive diarrhoea with the passage of blood-stained mucus in the stools, in severe cases general constitutional symptoms due to absorption of toxins and, occasionally, intractable vomiting are noted. The tongue is usually dry and furred and the pulse rapid and out of proportion to the degree of fever.

*Incubation period*—Whenever bacillary dysentery appears in a crowded community it spreads with alarming rapidity. The incubation period, as determined by the experiments which have been undertaken on man in the few instances recorded, is generally from three to seven days. According to Dudgeon the known incubation period in one case was twelve hours, in others thirty-two hours to six days. In laboratory infections (Hirschbruck and H. Thiem) it is usually three days.

*Onset*—Symptoms usually begin suddenly, abdominal pain and discomfort with colic are felt some time before the initial diarrhoea begins, accompanied by violent and excessive peristalsis, and usually diarrhoea persists for a day or more before blood and mucus appear in the stool.

E. Becher (1918) considered that there are characteristic differences between the clinical course of Shiga dysentery and that due to Flexner, so that the latter is not to be considered merely as a slighter form. Flexner dysentery, he thinks, begins quite acutely with a high fever of short duration and simultaneously, or soon afterwards, diarrhoea sets in, with blood and mucus in the stools. Rigors and vomiting are also often observed at the commencement of the disease which, on the average, runs a course of one week.

Shiga dysentery begins less acutely and increases in severity, reaching its climax only after some days. The fever, when present, is of longer duration than in Flexner infections, and the initial sharp rise is missing. On the whole, the duration of the disease is longer. As a general rule, too, the condition of the patient in Shiga dysentery is graver and the prognosis worse than in Flexner dysentery. This worker claims to be able to differentiate the two forms of dysentery on their clinical course alone, but this is doubtful.

H. W. Corner has emphasized that in Shiga infections there is an early histotoxic anoxæmia, manifest as a peculiar bluish flush which soon gives way to pallor. Early exhaustion is due to toxæmia, while late exhaustion results from tissue depletion. Hypotension is a feature of special note. Usually there is a marked fall of systolic pressure, which for weeks remains below 110 mm Hg.

*Pyrexia*—Fever is an accompaniment of all cases of bacillary dysentery except in mild attacks. Generally it is of a low type, i.e.

from 99°-100° F (37.2°-38.8° C) but in the more acute cases the temperature rises to 103° and 104° F (39.4°-40° C) at night. The fever may be of an intermittent or even of a remittent type and the continuation of the pyrexia in convalescent patients may be regarded as a sign that considerable destruction of the mucous surface has taken place. Sometimes the fever is so high and the toxic appearance of the patient so marked that bacillary dysentery may simulate typhoid. On the other hand absence of fever is by no means a propitious sign. In toxic cases collapse with subnormal temperature may usher in the disease and the outlook then becomes grave.

*Abdominal pain and tenesmus or straining*—The gripping abdominal pains due to violent and unrestrained peristalsis are very intense and distressing. The pain is generalized over the whole abdomen and attempts at palpation elicit tenderness especially on deep pressure. The area involves the small as well as the large intestine while intense straining or tenesmus denotes that the pelvic colon and rectum are severely affected. The spasm of the rectum may last for half an hour after the passage of the stool or it may be continuous and so distressing that the patient becomes exhausted. In mild cases it may be absent altogether. Rectal prolapse may be a sequel.

Dysuria or strangury is often present and adds yet another distressing feature to this unpleasant disease. Its origin may be reflex and probably originates in spasm of the bowel in the vicinity of the bladder. Death may take place quickly but usually two to four weeks elapse.

*Palpation of the abdomen*—Usually quite early in the course of dysentery probably owing to inflammation of the intestines the recti muscles are so rigidly contracted that palpation of the abdomen becomes difficult but later especially in cases of great severity the abdominal wall is more lax. Frequently when the pain passes off and sensation is blunted by toxic absorption prognosis becomes graver. The spastic contracted loop of the sigmoid colon becomes palpable and can be rolled like some pliable rubber cord beneath the examining hand. In contrast to the amœbic form transverse colon and cæcum are not contracted to such a degree and so cannot be readily discerned.

*Character of the stools*—It would probably be more correct to describe the discharge from the bowel in bacillary dysentery as exudate rather than a stool. The frequency and character of the evacuations may be taken as guides to the progress of the case. In number they may vary in the twenty-four hours from two or three to fifty or they may be uncountable—in other words the unfortunate victim may be glued to the commode.

In the early stages during the first three days evacuations consist of blood stained mucus which is gelatinous and adheres to the bottom of the bed pan or other container in appearance it has been variously compared to pink frog spawn or to red currant jelly. It is practically odourless or may give off a faint smell of spermin. After a period of three or four days the stools become more purulent that is to say they

are mostly composed of pus cells, and blood is less apparent. In the next stage, bile pigments appear together with liquid grey faecal matter, later still during convalescence, the faeces become yellow or brownish.

The colour and consistency of the faeces, when the spasm of the sigmoid colon has passed off, vary considerably according to the diet. Should the patient be fed on milk, solid casein curds and undigested portions of food are noted. In mild cases fluid faeces may be passed from the commencement, together with blood and mucus. In Flexner infections the exudate may, from the commencement consist entirely of mucus without admixture of blood, so that it is not necessary for the latter to be present before a diagnosis of bacillary dysentery be justifiably made. In the most acute and fulminating cases stools contain a large proportion of dark and decomposed blood. They have been compared to 'meat washings', exuding a kind of stale musty odour, or they may consist of blood stained clots with a background of green, bile stained mucus, betokening grave prognosis. In very rapidly fatal cases no blood or mucus may be noticed in the stools from the commencement but they consist of a foul fluid containing much altered blood but without admixture of mucus unless one is familiar with the underlying pathology, stools such as these may be mistaken for ptomaine poisoning or some choleraic condition.

The following table demonstrates in a dogmatic manner the main differences between the stool of acute bacillary dysentery and that of the corresponding stages of the amœbic disease —

<i>Acute Bacillary Stool</i>	<i>Acute Amœbic Stool</i>
Blood and mucus	Blood and mucus intermingled with faeces
Mucus tinged with bright red blood throughout, viscid, adhering to bottom of pan	Fluid mucus not adhering to pan, blood generally dark red, in streaks or clots
Odourless. An acute inflammatory exudate derived from the mucosa of the whole or major part of the large intestine	Strong fetid odour, probably due to bacterial contamination and decomposing blood. Derived from the sloughs of ulcers together with exudate and intermittent hæmorrhage. Comparable with anchovy sauce

*Blood changes* — It appears, from work that has been performed on the blood appearances in bacillary dysentery, that there is no alteration in the hæmoglobin content or the number of red blood corpuscles in the early stages of the disease. In fact, the cell volume, according to R. Gantenberg (1939), may be raised owing to dehydration. Generally speaking there is no rise in the total number of leucocytes or in their relative proportions except when the inflammation of the bowel has persisted for a considerable time. Then, apparently, a moderate leucocytosis of from ten to fifteen thousand per cubic millimetre may

be present Laempe (1918) records that there are usually about 18 000 leucocytes with a rise in the polymorphonuclears. In the chronic form secondary anæmia is usually noted.

**Urine**—In severe cases the urine is of high specific gravity, about 1,030, concentrated, dark coloured, and contains a heavy deposit of urates. No albumin or any other abnormal constituent is present, except perhaps in the fulminating cases, where there is an increase of indican.

**Classification of the different types**—On clinical grounds the forms of bacillary dysentery encountered may be classified as follows: (a) mild, (b) acute, (c) fulminating, (d) relapsing, and (e) chronic.

(a) *Mild or abortive type*—In the milder types, which are usually Flexner infections, constitutional symptoms are either entirely absent or not very severe, and there is no fever. The motions may be composed of faeces from the commencement, or may contain a small quantity of blood and mucus.

It is unusual for more than six or eight motions to be passed in the twenty-four hours. Even in these mild cases the spastic sigmoid can be felt in the left iliac fossa. The tongue may remain clean and the pulse rate normal. The total duration may not be more than three or four days, and the patient convalescent at the end of the week. Acclimatization diarrhoeas, which are common in Egypt, India, and the Far East, and which are known by local names such as 'Gippy tummy,' 'Hong long Dog,' 'Simla Trots,' etc., come into this category, and are caused by infections with either Sonne or Flexner bacilli.

(b) *Acute type*—In acute cases the onset is much more abrupt. Within a few hours the temperature may be raised to 101°–103° F. The patient is obviously suffering from intestinal toxæmia, for his face becomes pinched and anxious—manifestations of severe dehydration. Defective absorption leads to chloride deficiency and tetany. Rigors are uncommon. Mental confusion and slight delirium may at first suggest enteric infection. Usually, within three or four hours violent diarrhoea sets in, the faecal discharges being replaced by typical dysenteric stools. As a general rule the stools exceed twelve in the twenty-four hours, and may retain their blood-stained character for at least fourteen days. Anorexia is usually present. The tongue is almost invariably coated with a thick yellowish fur, and the pulse rate is accelerated, in fact, tachycardia is present out of all proportion to the pyrexia. Tenesmus is a most distressing feature, especially during the night, and is usually accompanied by dysuria. The abdomen is navelicular, and on palpation the spastic colon can be distinguished. The duration of this form is usually about three weeks.

It is most important that this type of case should be immediately recognized, for, unless properly and thoroughly treated, it may relapse into the chronic, intractable form.

(c) *Fulminating or severe type*—This includes the most severe infections and can be divided into sub groups (1) the choleraic, and (2) the gangrenous. In both prognosis is extremely bad.

(1) The Choleraic Form—This form is somewhat rare, but, owing to superficial resemblance to cholera, the need for early recognition is obvious. The onset is generally acute, with vomiting, and collapse with attendant phenomena setting in early, but may be more gradual with severe headache and anorexia. The face is pinched, the eyes are sunken and expression anxious, the temperature is subnormal, the tongue dry and glazed, the skin of the extremities cold and clammy with tetanic cramps, the pulse small, rapid and thready. The abdomen, at first acutely tender becomes less so as toxæmia increases. Dysuria is usually acute. According to H. Otto (1940), the *facies Hippocratica* and extreme emaciation present a picture so like Simmonds' disease as to suggest an adrenalin syndrome.

The loss of fluid from the body is so rapid that the specific gravity of the blood rises rapidly from 1.036 to 1.060. The initial discharges are profuse and watery, roughly resembling the stools of cholera, but may soon give way to a brown offensive fluid containing altered blood. Usually the appearance of collapse becomes more pronounced and death takes place within three days of the onset, but some who resist the first critical days appear superficially to do well for two or three weeks, then suddenly collapse and die.

(2) The Gangrenous Form—In this type the attack of dysentery commences suddenly, often accompanied by rigor, headache, vomiting, and other evidences of severe intoxication. The temperature rises rapidly to  $102^{\circ}\text{F}$  ( $38.8^{\circ}\text{C}$ ) or even  $104^{\circ}\text{F}$  ( $40^{\circ}\text{C}$ ). The face is flushed and feverish, the pulse at first rapid and bounding becomes weak and relatively slow, the blood pressure is so reduced as to register a systolic reading of 50 mm Hg.

The outstanding feature of this form is the severity of the abdominal pain, cramps and tenesmus, usually the transverse and sigmoid colon can easily be palpated through the abdominal wall. The temperature is intermittent, and tends to fall to subnormal on the fourth day. The tongue at first covered with a dense white fur soon becomes yellow brown, dry, and cracked. The abdomen is sunken and the stools which in the early stages resemble meat washings, are later converted to a dark grey offensive fluid containing much decomposed blood. A particularly characteristic appearance is the passage of dark greenish sloughs often of a considerable size which represent the exfoliated and necrotic mucous membrane. The stools are uncountable, with complete incontinence of urine.

The urine usually contains a cloud of albumin. \*Inflammation of the glans penis, a diphtheritic balanitis has been observed in severe dysentery epidemics (C. W. Daniels). As the strength fails, so the voice

Toxicæmic nephritis as described by N. H. Fairley in Palestine is accompanied by casts, high blood urea and obvious signs of nitrogen retention.

becomes husky, and collapse sets in. Severe cerebral symptoms are common, and psychoses were observed in the Polish epidemic (1939).

In this form the body may emit a musty odour, which becomes more intense as the disease progresses.

(d) *Relapsing bacillary dysentery*—It is usually stated in textbooks that relapses are not found in bacillary infection, but this is incorrect. In cases of the acute type which had not been thoroughly treated, relapses, with characteristic stools from which bacilli could be isolated, were noted frequently during the 1914-18 War, usually occurring at the advent of cold weather or as a sequel of some unaccustomed physical exertion. Unless adequately treated this type is apt to emerge into the chronic form.

(e) *Chronic bacillary dysentery*—This form of dysentery in soldiers demobilized since the 1914-18 War received considerable attention. They are victims of chronic ulceration of the mucosa which has already been described. Chronic bacillary dysentery is really a form of chronic diarrhoea with recurring exacerbations and occasional passage of blood and mucus, persisting for months or it may be for years and is particularly intractable.

Diarrhoea due to chronic dysenteric infection has been recognized in India for many years under the synonym of *Morbus Bengalensis* (Chevers 1886), and accounts for an almost unbelievable emaciation in coolies in India and Malaya. Intestinal symptoms may become exacerbated at intervals, sometimes with the passage of blood and mucus-stools and chronic diarrhoea. As the disease progresses, secondary anaemia becomes evident, with cardiac failure and oedema of the feet. The sunken abdomen and extreme emaciation form a striking clinical picture. Death usually occurs from exhaustion or from intercurrent disease, or may be due to hæmorrhage from the ulcers, while perforation of the bowel with peritonitis occasionally occurs. The difficulties in making a correct diagnosis are increased by the fact that it is almost impossible to culture dysentery bacilli from the stools.

J. Strasburger (1921) has found it difficult to estimate, in a disease of such varying intensity as bacillary dysentery, the exact proportion of cases which become chronic. It is rare, he thinks, to find chronic bacillary dysentery commencing as a relapse after apparent recovery.

Distinction must be made between the ulcerative and dyspeptic forms of bacillary dysentery. Some cases of chronic bacillary dysentery resemble ulcerative colitis, the patients continuously passing liquid faeces intermingled with blood and mucus. The dyspeptic form is also fairly distinctive, and symptoms referable to disturbance of gastric function follow immediately upon the acute attack (see p. 74).

Stenosis of the large intestine may take place as a sequel to chronic bacillary dysentery, but is rarer than is usually thought. In one such case of the author's, narrowing of the lumen of the sigmoid colon was found.

There is a form of chronic bacillary dysentery which closely resembles granular rectitis (see p. 440). In this form the general condition of the

patient is good, but a granular zone extends 2-3 ins up the rectum, which has failed to heal. The patient continues to pass blood and mucus after each formed motion. This condition may persist for more than a year subsequent to the acute attack of bacillary dysentery, it is usually amenable to bismuth subgallate retention enemata (see p. 453).

**Special features of bacillary dysentery in the 1939-40 campaign**—In addition to the work of Otto and Gantenberg K. Steuer (1940) has described special features of the epidemic of bacillary dysentery in the German Army during the Polish campaign. There were 1,200 cases, with 8.8 per cent mortality incidence, and the epidemic was characterized by the rapidity of its spread. The factors concerned in this are said to have been—the endemicity of the infection, general lack of sanitation, mobile warfare, season of the year and contaminated water, added to flies and prolonged exhausting marches. The inability, on account of existing conditions, to house the hospital staff in separate quarters, caused the infection of 5 out of 10 physicians, 4 out of 12 nurses and 8 out of 42 sanitary personnel.

In two thirds of the series there was typical dysentery with bloody mucous stools. In 26.6 per cent the condition was serious, in 6.6 per cent extremely so, with cerebral involvement, pronounced dehydration, flabbiness of skin, cracked lips, brown discoloration of tongue and deeply sunken eyes. Herpes of lips was common and hiccup always an unfavourable sign. Damage to circulation was seen with all serious infections: pulse rapid and feeble, collapse frequent and not responding to medication. Early death, usually in the second week, was associated with vasomotor paralysis.

Only 9 out of 40 patients who died were received in hospital within 3 days of onset, but almost half were admitted after the first week. 80 per cent of those received within the first three days were discharged within four weeks. Anal swabs (bacteriological tests) in 390 cases gave 18.5 per cent positive and 81.5 per cent negative for dysentery bacilli. Injection of antidysentery serum produced therapeutic effects on circulation, pyrexia and tenesmus and several subchronic conditions were benefited by serum enemata.

Complications were proctitis, disorders of bladder, rheumatic manifestations, conjunctivitis and intermittent fever. Pronounced arthritis was seen six times. Oedema was frequently noted. Major intestinal hemorrhages resulting in anaemia were noted three times.

**Latent dysentery**—J. Cunningham (1918) concludes that a latent form exists in which the stools may exhibit varying quantities of mucus, or mucus and blood containing dysentery bacilli—a state not incompatible with good health and on this account cases may escape detection. A macroscopic examination of the stools for mucus, or for mucus mixed with blood, forms a convenient method for their detection, and is more simple and effective than a bacteriological examination. Similarly an estimate of the degree and extent of dysentery prevailing in native populations can be formulated.



**Bacillary dysentery in small children**—In the tropics bacillary dysentery is especially apt to attack small children under five years of age, and is to be regarded as a serious disease. As a general rule it may be stated that it is much more acute and severe in European children than in those of native races. The disease apparently can be spread by milk which makes careful supervision and sterilization necessary. In young children the symptoms of toxæmia are much more sudden and acute and may overshadow the bowel symptoms. The attack may be ushered in with convulsions and the child may die in coma.

It has now come to be recognized that many of the epidemics of summer diarrhoea in the great cities of North America and Canada even those of Europe are due to infection with Flexner bacilli therefore such cases should be recognized early and treated as if they were examples of bacillary dysentery. Epidemic infantile diarrhoea is known in Japan as *Fukin*. This epidemic acute disease of infants with sudden onset fever mucous diarrhoea sanguineous stools cramps and collapse prevails mostly in summer sometimes in spring and autumn. Death or recovery may follow within twenty four hours of onset and mortality varies between 39 and 82 per cent. Sucklings are said never to be affected. Possibly collapse may be ascribed to suprarenal insufficiency. Treatment is by subcutaneous injection of adrenalin 0.3 to 0.5 c.c. of 1:1000 solution which is an effective remedy (K. Kawata 1925).

K. Kiyono and N. Okubo (1917) M. Minoda (1921) and S. Tawara (1921) have written on this subject as it affects children from two to six years of age in Japan. In these small children the dysentery toxin is especially apt to attack the central nervous system and the brain. In about 1 per cent. of cases *Shiga's bacillus* has been isolated but K. Adachi (1921) has brought forward evidence that *Sonne's bacillus* may also sometimes be the cause.

W. C. Davison (1920) in a series of 134 cases of dysentery and diarrhoea in children varying in age from three months to eleven years in Baltimore found that in one series of 71 cases there were fifteen deaths—a mortality of 21 per cent. Out of thirteen cases from which a satisfactory stool specimen was obtained Flexner's bacillus was obtained in six *Shiga's bacillus* in one. Altogether evidence of infection with *B. dysenteriae* of one kind or another was shown in 83 per cent. of cases of clinical dysentery in hospital. The ratio of Flexner to *Shiga* infections was 8:1.

O. Lade (1921) had the opportunity of studying 143 cases of bacillary dysentery in children in a clinic at Dusseldorf in Germany. Thirty three cases only were positively diagnosed and in 9 *Shiga's bacillus* was identified. The seasonal incidence of bacillary dysentery in children was very marked. In 1919 the highest point was reached in October and in 1920 in July. House to house infection undoubtedly took place. The case mortality diminished with increasing age for the first two years of life it was about 80 per cent.

G Kuntze (1921) records a summer and autumn epidemic of bacillary dysentery in 143 children, of which 85 were infants and 58 over eighteen months of age. The clinical picture of the disease was by no means constant and the differentiation from the milder forms of diarrhoea was not generally easy.

H Schelble (1918) studied the gradual spread of dysentery amongst the civil population in Germany during the 1914-18 War. In Bremen especially there was an increase of dysentery cases in the Children's Hospital. From July to September, 1917 there were 82 cases with 21 deaths, a mortality of 25 per cent.

**Asylum dysentery**—Asylum dysentery can hardly be considered as a special clinical form of the disease, but for a long time it has been known that the form to which the feeble minded are specially liable in English and Continental lunatic asylums is really a mild infection with dysentery bacilli while attendants on these cases are apt to be attacked. Acute and fulminating types are rare and the chronic form is frequently encountered.

In the majority of cases according to H S Gettings Flexner bacilli are responsible but more recently Sonne's bacillus has been isolated. Probably insanitary habits of the insane, their enfeebled constitution and the breaking down of their natural resistance to disease are responsible for the spread of the infection. The existence of bacillary carriers in most British asylums has been abundantly demonstrated.

In a report presented to Parliament in 1842 dysentery was recorded all over the Kingdom by the Poor Law Officers with the sanitary zeal and reform of the fifties the filth was swept away and dysentery disappeared to remain in the lunatic asylums.

In 1911 there were in English asylums 1,457 cases with 818 deaths; in 1912 1,555 cases with 287 deaths; in 1913 1,159 cases with 270 deaths.

During 1919 in eighty country asylums there were 1,722 cases of whom 20 per cent died—forming 8 per cent of the total number of deaths. Contrary to the generally accepted view that bacillary dysentery is a summer disease, the highest incidence of cases in Claybury occurred during the winter months.

F W Mott in 1901 and 1902 made a careful study of the disease from a clinical and epidemiological viewpoint in this country.

H S Gettings (1915) was able to trace the dysentery history of Wakefield Asylum (West Riding Mental Hospital, Yorks) since its opening in 1818. Almost from the commencement dysentery made its appearance and it has lingered on there ever since. Sanitary measures of all kinds were adopted but all have uniformly failed. In 1911 there were nearly three hundred dysenteric cases.

J S Bolton and M J McGrath (1922) following the work of Gettings, were all too ready to report that as the result of special measures the disease was becoming increasingly rare in British lunatic asylums.

In Scottish asylums the disease appears to be rare, possibly because they are not so overcrowded.

It is probable that in asylums epidemics are kept up by carriers, who are particularly difficult to detect. Relapsing cases of dysentery are also probably responsible. It was found at Claybury (London) that, out of 590 patients who have suffered from dysentery during the last twelve years 18 per cent relapsed once, 6 per cent twice, and 3 per cent three times.

F. H. Lorentz (1919) gives an account of an outbreak of dysentery in the asylum at Duren, Germany, which was brought to a close by a systematic search for chronic carriers. Four were discovered and by their isolation and the surveillance of all contacts, the outbreak was suppressed. The uncleanly habits of the insane greatly facilitate propagation in asylums and, moreover, the type of dysentery is usually of a larval character, so as to escape early recognition. The mortality is fairly high as the disease shows preference for old and debilitated patients.

E. T. Hillard (1925) described bacillary dysentery as being endemic in the mental hospitals in Australia, at times flaring up into epidemics which are extremely difficult to eradicate. The main clinical types to be distinguished were mild relapsing and toxic. The organisms were isolated from the stools in 70 per cent of the acute cases, and proved to be *Shiga* 10 per cent, *Flexner* 30 per cent, and the *Y* bacillus 85 per cent. The prevention of this disease in asylums consisted of quarantining newcomers for three weeks and of the isolation of all cases of diarrhoea and dysentery, and carriers for as long as possible.

### SHIP-BORNE DYSENTERY AND DIARRHOEA

The development of inter oceanic and air borne travel makes the subject of diarrhoea and dysentery contracted in transit a matter of importance and interest. This subject has attracted the notice of general practitioners during recent years on account of the increasing popularity of organized cruises to the tropics. To some degree also the comparative cheapness of these tours has increased the opportunities to visit many hitherto unfrequented spots in the Aegean Sea, and has thereby enlarged the possibilities of contracting dysenteric infections.

Undoubtedly the most common infection contracted in this manner is bacillary dysentery of the *Flexner* type due to contamination, either fly borne or food borne, of some meal eaten at a wayside restaurant, the most dangerous articles of food in this respect being fresh salads or fruits. Bacillary infection contracted on shore becomes manifest on shipboard two or three days after putting to sea.

During 1936 a sustained correspondence on the subject appeared in the *British Medical Journal*. J. B. Hern, in a somewhat alarmist article, described several hundred cases on a pleasure cruise of fourteen days' duration. Dysentery with pyrexia ( $103^{\circ}$  F.) appeared forty

eight hours after the commencement of the voyage. In the bacteriological investigation of one patient who had not recovered on her return to England, Flexner's bacillus was discovered, subsequently she suffered from two relapses.

H. M. S. Turner thinks that the risk of contracting bacillary dysentery on such a pleasure cruise, during visits to places of interest on shore, is considerable, there being special risk at Alexandria and Port Said.

A. A. Kloss thinks that, on voyages to India at any rate, risks have been greatly exaggerated. Most of the cases of dysenteriform diarrhoea are due to over-indulgence in unsuitable food on board ship. He stresses the difficulty of differentiating these cases from true bacillary dysentery, especially in the early stages.

The following is a summarized account of instances of this nature which have come under the author's personal observation —

(a) A woman of fifty five, seen in September, 1933, on return to England from Majorca. Commenced dysenteric symptoms on board ship with pyrexia and passage of blood and mucus. Loss of weight. Faeces blood and mucus—typical bacillary exudate. Serum agglutinated *Shiga's bacillus* 1. 200.

(b) A man of forty eight, seen in November, 1935, on his return from Teheran, Persia, contracted bacillary dysentery and continued to pass blood and mucus on passage through Mediterranean. On arrival in England was still passing blood and mucus stools. Bacillary dysentery exudate, probably a Flexner infection.

(c) A man of thirty one, seen on arrival in London in January, 1936, from a pleasure cruise from Aden, where he apparently contracted bacillary dysentery, which became apparent in the Red Sea, three days out. Pyrexia, blood and mucus in stools. Was treated as a case of amoebic dysentery. No evidence of this infection ever obtained. On arrival in England stools still contained blood and mucus. Serum agglutinated *Flexner's bacillus* 1. 800.

(d) A retired Colonel, aged sixty nine, had been on a trip to Khartoum. Developed acute dysentery on Nile steamer and was extremely ill at Juba. Flown to Entebbe by air, and treated as case of acute amoebic dysentery, with emetine injections. Became very emaciated and extremely ill. Arrived in England, April 1935. Serum agglutinated *Shiga's bacillus* 1. 400.

(e) An engineer contractor, seen in August, 1925, employed erecting a dam on the Blue Nile for two and a half years. Apparently contracted Shiga dysentery at Port Sudan. Dysenteric symptoms commenced when three days out at sea. On board ship he was treated as a case of amoebic dysentery, with emetine injections. On arrival in London was passing blood and mucus stools with characteristics of bacillary dysentery. *Shiga's bacillus* isolated from faeces as well as from surface of rectum.

(f) A cadet in Colonial Government Service, who had contracted dysentery in North West Territories of Gold Coast, had been ill for two months and had been treated with emetine injections. Relapse with blood and mucus on board ship. Was treated as amoebic dysentery. On arrival in England in July, 1933, was passing blood and mucus in stools. Bacillary dysentery exudate. Serum agglutinated *Shiga's bacillus* 1. 200.

(g) A woman of thirty one, seen December, 1934, on return from India,



1 1 M 1



2



3

- 1 Acute Shiga Dysentery showing intense edema of mucosa and submucous hemorrhages in transverse colon 2 Acute Sonne Dysentery in a child (Dr N H Fairley's case) showing bright pink hyperemia of ascending colon 3 Ulcerative Colitis showing destruction and ulceration of the mucosa, laying bare the muscular coat (lower sigmoid and upper rectum)

## PATHOLOGICAL CHANGES IN THE LARGE INTESTINE

she contracted some form of acute dysentery in May, 1934. Treated as amoebic dysentery with emetine injections. Dysenteric attacks, accompanied by pyrexia. Loss of 14 lb in weight. Relapse on board ship. Faeces contained blood and mucus, bacillary dysentery exudate. Serum agglutinated *Flexner bacillus* 1 200.

Some cases are doubtless due to Sonne's bacillus, and the danger of food borne infection on shipboard has not been sufficiently recognized.

In March, 1934, the author investigated the case of a woman who had developed dysentery, with passage of blood and mucus, on board ship, and had suffered from three distinct attacks with some pyrexia and abdominal pain, during the voyage. Her boy of three, who shared the same cabin was similarly affected. The faeces of both consisted of a typical bacillary dysentery exudate. The serum of both agglutinated Sonne bacillus emulsion 1 100.

The author has seen a good many cases of white diarrhoea with sprue like stools commencing on board ship. The other accompaniments of sprue, such as wasting, sore tongue and anaemia were absent. In one instance it was ascertained that the original infection was Sonne's bacillus, which, it must be noted, may produce a clinical condition simulating temporarily the clinical features of sprue. Thus by no means negatives the fact that many cases of sprue do originate at sea. Sprue diarrhoea on board ship is not confined to European officers, but may also—though rarely—originate in white and occasionally in Indian seamen. Among passengers especially on the voyage from India or China, sprue may make its appearance for the first time on board ship. Very often the onset is violent, and emaciation may be extreme. In September, 1936, the author examined a planter from Malaya with sprue like diarrhoea and characteristic stools. The illness commenced ten days after leaving Japan and persisted throughout the voyage.

Other cases of ship diarrhoea resemble mucous colitis (see Chapter XXIII) and may be the sequel of a bacillary dysentery infection contracted on shore. A similar form is also frequently seen in small children. The author's experience also points to the possibility of coeliac disease making its first appearance in children from the tropics when on board ship. The clinical appearance of these children is quite characteristic, with pasty complexion and turgid swollen abdomen. The coeliac affection has a disturbing effect upon temper and mentality, the children becoming a trial to their parents. The exacerbation which becomes apparent on the voyage may be due to unsuitable dietary, though change in temperament and appearance when on a fat free diet is remarkable.

The author has not encountered amoebic dysentery contracted at sea, but he has seen many instances where the infection was acquired ashore, and gave rise to symptoms for the first time on board ship. These patients, as a rule, contracted the original infection in India and the Far East.

## SONNE DYSENTERY

A full account of the bacteriology of Sonne's bacillus is given in the Appendix (p 561).

Recent work on Sonne infections in England and other countries has brought to light a new clinical entity. Particular prominence is given to the very varied clinical pictures which this bacillus may provoke, and which differ in many respects from the clearer cut dysenteric syndrome of Shiga and Flexner. The pathological appearances somewhat resemble those of the latter type (Plate IV, 2).

Probably mild attacks of dysenteriform diarrhoea are the rule in most cases. In the early stages the faeces are greenish, with blood flecked mucus from which almost pure cultures of late-lactose-fermenting organisms (Sonne) may be obtained. Confirmation of their identity with specific serum is readily produced.

The most comprehensive descriptions of the symptoms are those by A. M. Kinloch and J. Smith in 1926. In one class of case the symptoms approximate to those of an acute Flexner dysentery, with sudden onset of illness, diarrhoea, colic, and the appearance of blood and mucus in the stools. In a second they may assume a more alarming aspect and approach in virulence those of the Salmonella group. J. A. Charles and J. H. Warren (1929) describe cases with sudden onset, vomiting, and diarrhoea with the passage of "tomato soup" stools, more nearly resembling the choleraic form of Shiga dysentery, followed by rapid prostration. But in the great majority of Sonne infections, the symptoms appear suddenly, resembling an irregular diarrhoea, with greenish mucoid stools.

In all Sonne infections there is a tendency to pyrexia associated with an abrupt onset, but in the milder cases the fever is slight and transient. One remarkable feature is the association with diarrhoea of catarrh of the respiratory system which not infrequently precedes the development of abdominal symptoms, it is co-terminous with them, and apt to occur more frequently in children than in adults.

R. Crumckshank and R. Swyer (1940) have well described a recent epidemic in which some cases showed an initial rise of temperature varying from 98.8–104° F, averaging 100° F, but most were apyrexial. Sometimes pyrexia may be due to superimposed causes, such as mastoiditis or appendicitis. Intestinal symptoms are not generally severe, but toxic cases may sometimes be observed, and the author has treated several cases which resembled severe Shiga infection with dehydration. The commonest type of stool in this epidemic was loose green and mucoid. A slightly higher proportion were alkaline than acid. A smaller number passed typical dysenteric motions. Rhinitis was present in ten children, otitis media in three, but bronchitis was common.

The stools usually number 5–8 in the twenty-four hours, and the abdomen shows slight distension. Acute symptoms usually endure for forty-eight hours and are followed by a feeling of lassitude and lethargy,

stools remain loose and greenish, but in the next few days become brown, formed and more normal

E Harvey has reported that very acute Sonne infection in children up to nine years of age may be the cause of sudden death

The paper by J A Charles and J H Warren (1929) indicates how widespread this infection may be in England as a result of acute attacks of 'food poisoning,' a point to which W G Savage and P B White first drew attention in 1928. An outbreak described by R E Smith is interesting because some cases were of this acute type

One of the best described outbreaks of food poisoning due to Sonne's bacillus occurred in St Pancras and Holborn, London (G Snowden, 1933). Here 13 people were attacked: 11 in St Pancras and 2 in Holborn. Five were adults, eight children, and two of the latter, aged 11 and 13, died.

The clinical symptoms were vomiting, acute abdominal pain with passage of blood and mucus in the stools, and, in some cases, a high temperature. The sudden onset pointed strongly to food poisoning and it was found that they had all eaten 'pease pudding' which had been purchased at a certain shop in St Pancras the previous night. This had been prepared from dried peas boiled with sodium bicarbonate, and bacteriological examination revealed large numbers of Sonne's bacilli. At the inquest it was ascertained that about twenty people had partaken of it and the evidence proved, as far as proof was possible, that a girl, who was found to be a carrier, had contaminated the pudding.

A M Fraser, J P Kinloch and V J Smith (1926) in the routine examination of enteritis cases in Aberdeen, found 33 of Sonne dysentery, most of them in institutions where the inmates were under strict medical observation. The blood serum of 31 cases, taken between seven and twenty days from the onset, gave a positive agglutination in dilutions varying from 1:50 to 1:6400.

G M Fyfe (1927) has described a milk-borne epidemic of Sonne dysentery at St Andrews between September 5 and September 26. The total number of cases was estimated at nearly 200 and there were no fatalities. The incubation period was shown to be probably less than twelve hours. The respiratory catarrh which was such a feature of the Aberdeen outbreak was not noticed. Usually recovery was complete in a week.

A similar outbreak has been described by G Abraham (1929) in seventy cases in Frankfurt am Main. Toxic symptoms in the form of unconsciousness, convulsions, and delirium were present.

The year 1937 witnessed a remarkable increase in the number of dysentery cases of the Sonne type in this country, recorded in many quarters, but mostly in the London area. Possibly this was due to the improved methods of diagnosis and the more general appreciation of Sonne's bacillus as a pathogenic agent.

There has been a general increase in the figures in the Registrar General's weekly return for the last few years, but towards the end



of 1937 a very marked increase was noted, for the week ending December 4, 1937, there were 454 cases. The figures for 1935 and 1936 were double and treble those for 1934, while those for 1937 were ten times that number. In passing it should be remarked that, judging from the returns of the Health Section of the League of Nations, the same tendency to increase is shown in many European countries, in Germany, for instance, the summer figures for 1937 are almost double the mean values. E. Bloch (1938) has drawn attention to the great increase in Sonne dysentery in Glasgow in institutional as well as non institutional environments. Towards the end of 1937 the first large outbreak of this type of dysentery was recorded. Most of the cases were very mild.

J. J. Laws (1936) has described an outbreak in a mental institution in Epsom, Surrey. Apparently Sonne infection is specially likely to attack the insane and to spread with great rapidity among them. The onset was acute though the course was benign. Most cases soon became free from infection, but a small number continued to pass the organisms in the stools without showing any clinical symptoms. In mental asylums both these forms of "carrier" play a considerable part in spreading Sonne dysentery. From 30 per cent. of the cases Sonne's bacillus was isolated. The agglutination of the serum was positive within a fortnight of the onset in a dilution of 1/25 to 1/600.

The last two years (1939-41) have witnessed further widespread epidemics in England, and it has proved a definite factor in dysentery outbreaks in the Middle East.

**Diagnosis**—Diagnosis is easy in Sonne dysentery as the organism can usually be readily isolated from the stools. Cruickshank and Swyer stress the value of rectal swabs in obtaining positive cultures. In a total of 79 they obtained the following figures—

Fæces + and rectal swab +	36
Fæces —, rectal swab +	31
Total fæces +	45
Total swabs +	70

Therefore, by repeated examination of both faecal specimens and rectal swabs Sonne's bacillus can be isolated from most clinical cases, but the rectal swab method gives a much higher proportion of positive results. This organism is present in the intestine in a gradually decreasing proportion after the subsidence of acute symptoms. Convalescent carriers play an important part in the spread of infection. Three negative swabs are necessary before discharge. Serum agglutination tests have a definite diagnostic value in a few instances, but repeated tests have shown conclusively that sera initially negative remained so, while positive cases remained positive.

**Spread of Sonne dysentery**—G. K. Bowes (1938), in reporting an epidemic of Sonne dysentery in Bedford, has been able to demonstrate that the outbreak in this case was definitely *mill borne*. The organisms

were isolated from the milk as well as from the faeces of the patients. Fifty nine out of 106 households were affected.

#### COMPLICATIONS OF BACILLARY DYSENTERY

**Dysenteric arthritis**—This complication appears to have been known to Caelius Aurelianus who termed it '*rheumatismus intestinalis cum ulcere*'. To the older generation of physicians in India it was known as "dysenteric rheumatism". In many respects dysenteric arthritis resembles that of gonorrhoea and it is a curious fact that it is common in some epidemics and rare in others. In the Doberitz epidemic in Germany in 1900, arthritis developed in 8.75 per cent. of all cases, in 1897 in a similar outbreak in the Fiji Islands (C. W. Daniels) it occurred in 10 per cent., although in the same locality in 1910 in a series of 300 the author did not see one.

B. G. Klein (1919) recorded eight cases out of a series of 978 in Rouen. The knee joint was involved in every case, and the onset of the arthritis was about the twentieth day. The usual limits are the sixth to twenty-third days. According to Z. Cope (1920) in his experience in Mesopotamia, 1 to 2 per cent. of bacillary cases developed joint trouble, and this complication occurred up to three months after the primary attack.

Usually dysenteric arthritis is associated with Shiga toxins but in some cases a Flexner infection has also been noted but there are no records of it in the Sonne disease. The joint affection rarely develops in the acute stage of dysentery.

D. W. Ritchie, quoted by Cope, states that arthritis in the Salonica cases during the 1914-1918 War usually occurred during convalescence, he considers constipation to be a predisposing cause and states moreover, that those cases treated with frequent doses of tincture of opium were the most apt to develop arthritis.

An interesting fact is that there appears to be no correlation between the intensity of the arthritis and the severity of the initial dysentery. G. Graham (1919) believes that patients who show symptoms of arthritis early are more liable to severe attacks according to E. Stettner (1917) toxic conjunctivitis often precedes it.

G. Graham (1919) and Z. Cope (1920) agree that the knee is most commonly affected, in the series quoted by the former, both joints were attacked in sixteen cases, and one in fifteen, the ankles and elbows came next in sequence, and finally, in three cases the small joints of the wrists and hands. R. Gantenberg (1939) noted rheumatic sequelae in muscles, joints and periosteum, pre-eminently in the muscles of the left thigh.

Occasionally the temporo maxillary and sterno clavicular, and very rarely the hip joints, suffer. The affection usually flits from one joint to another with short intervals between. Different types of joint affection may be distinguished. The pains may be evanescent, and it is possible that the arthralgia is often situated in the fibrous muscle insertions.

*Hydrarthrosis*—In the knee a large effusion of synovial fluid may occur suddenly—it may be into the subcrureus pouch. The author noted that this is more likely to occur in rheumatic subjects. The effusions are usually accompanied by a rigor, by a rise of temperature to  $102-103^{\circ}\text{F}$  ( $38.9-39^{\circ}\text{C}$ ) and, in the initial stages, by pain, which, however, soon wears off, leaving stiffness, while the skin over the affected joint is shiny and reddened.

When aspirated, the inflammatory fluid is straw coloured, slightly viscid and usually sterile on culture, and it has the important property, as noted by B. G. Klein (1919) and S. H. Zia and H. J. Smyly (1931), of agglutinating the infecting dysentery bacillus (*Shiga* or *Flexner*) in a titre higher than that given by the blood serum from the same case. Apparently the joint effusion never becomes purulent, nor are the heart or valves ever affected.

There is some evidence, as noted by the author, that arthritis is more likely to develop in serum treated cases, and it becomes necessary to distinguish between dysenteric arthritis and fugitive poly arthritis which may accompany serum sickness (P. Manson Bahr, 1920; Z. Cope).

Dysenteric arthritis involving many joints may persist from a few days to six or eight weeks, but, however alarming this condition may appear at first to the patient and his medical attendants, it is comforting to know that permanent disability seldom ensues. Some disability is produced by the stretching of the joint capsule and the surrounding ligaments but, according to G. Graham, complete recovery may ensue even after this has persisted for six months.

In 1920 the author recorded arthritis associated with large, sterile effusions into the glutei and latissimus dorsi muscles which subsided slowly.

Z. Cope observed an ankylosing type with peri articular thickening more resembling rheumatoid arthritis. In this variety the effusion is less noticeable, and the inflammation seems to centre chiefly in the peri synovial sheaths. This results in considerable limitation of movement and may eventually lead to a more intractable disability.

**Eye complications**—Unilateral or bilateral conjunctivitis may be associated with the acute stage and, in convalescents, mdo-cyclitis ushered in by fever and rigors. These complications have been well described by G. Graham (1919) and E. Maxwell and W. H. Kiep (1918). According to the former, conjunctivitis was noted between the fourteenth and thirty fourth day of the disease, in one case as late as the eighty fourth. Dysenteric conjunctivitis yields rapidly to instillation with 2 per cent argyrol. These ocular affections may be accompanied by articular effusions.

Maxwell and Kiep lay stress on the frequency of anterior uveitis, as first pointed out by Morax. They describe adhesions to the capsule of the lens formed by a thin membranous film of exudate occupying the pupillary space and a number of opacities with a deposit of uveal

pigment arranged fringe wise round the margin of the membrane and also extending along those lines running radially between it and the edge of the iris

There is acute tenderness on pressure over the ciliary region, with photophobia, blepharospasm, and marked circumcorneal hyperæmia. The pupils are irregular with ring synechiæ. Iridectomy was performed in one case and the aqueous humour was found by J. A. Arkwright to agglutinate Shiga's bacillus. 180 G. Worms, P. Lesbre and G. Sourdille (1926) noted that, in dysenteric sclero conjunctivitis, the tears did not contain specific agglutinins. As a rule, iritis subsides *pari passu* with arthritis.

**Parotitis.**—This may be either uni- or bi-lateral, is painless, and is usually associated with joint complications. It is difficult to say whether it is of true dysenteric origin or whether it is due to septic absorption from the mouth. A particularly severe form ending in gangrene has been observed in Sumatra by J. Smits (1915).

**Portal thrombosis.**—This has been recorded and has led to portal pyæmia and miliary abscesses.

**Intussusception.**—Intussusception of the small bowel may occur in bacillary dysentery in children. It is very necessary that this complication should be early recognized for operative interference is the only remedy. A sudden increase in abdominal pain, together with vomiting and the disappearance of faecal matter, should suggest digital examination of the rectum for the characteristic tumour. It must, moreover, be remembered that intussusception may resemble bacillary dysentery and is frequently mistaken for it, and is also found post mortem as an agonal phenomenon.

W. G. Pridmore (1897) considered that dysentery, by its enfeebling effect on the intestines, aided by straining and peristaltic movements, is a predisposing cause.

**Thrush.**—In the tropics, infection of the mouth, the pharynx, and even the œsophagus, with the greyish growth of the thrush fungus is common, and in these cases large numbers of the characteristic yeast cells are present in the stools, and may cause them to assume a frothy bubbling character somewhat resembling those of sprue.

#### SEQUELÆ OF BACILLARY DYSENTERY

**Peripheral neuritis** may follow bacillary dysentery, as many other specific infections. This has been doubted, but the author has seen so many cases following on dysentery epidemics that he is inclined to believe there is some connexion. The legs are usually affected, with loss of knee-jerks, glossy, atrophic skin, œdema of the ankles, and hyperæsthesia of the calves. This condition may persist for several months.

A. Bittorf (1918) observed neuritis in 1 per cent. of cases in an extensive epidemic, he regarded it as a secondary toxic affection due

to absorption of bacteria and their toxins from the ulcerated bowel. Malnutrition and emaciation, which cause the disappearance of fat from the medullary sheath of the nerves, favour it. The majority of cases exhibited mainly sensory disturbances partly subjective and partly objective without trophic changes. Muscular spasm and cramps, especially of the calf muscles, were not rare, and only one case of severe motor neuritis had been seen.

A. G. Biggam (1929) recorded a case in which the sequence of events appeared to suggest that acroparæsthesia of the legs was due to dysenteric toxins. Rapid improvement followed on large doses of intravenous antiserum.

**Stenosis**—Stenosis is the result of great damage to the mucous membrane. The large intestine may be transformed, as in ulcerative colitis, into a narrow tube. Adhesions to surrounding organs may occur, and may give rise to distressing and painful peristalsis. Stricture of the colon must be excessively rare. A. Davidson recorded six cases only in thirty years' experience in India, and the author has encountered one single instance as the result of infection contracted during the 1914-18 War.

**Post-dysenteric constipation**—This is frequent after the subsidence of an acute attack, and is possibly due to the resulting atony.

**Hæmorrhage**—Massive intestinal hæmorrhage from ulcers has been recorded in the chronic form.

**Achlorhydria**—A. T. Hurst (1915) suggested that the high incidence of bacillary dysentery in the troops at Gallipoli might be due to a temporary achlorhydria. In 1920 H. Strauss reported that twenty-one out of a hundred cases of bacillary dysentery had achlorhydria which was attributed to the infection. F. F. Camps (1938) has published the result of test meals of a hundred post-dysenteries under the Ministry of Pensions. He found either complete achlorhydria, or a slow rising type of curve. This factor was held responsible for many digestive troubles following bacillary dysentery. In the author's series of post-bacillary dyspepsia achlorhydria and hypochlorhydria have been found to be the rule.

**Tachycardia**—Owing to the physical exhaustion of the patient, and possibly also to toxic myocarditis, a condition of irritable heart persists long after dysenteric symptoms have disappeared. In those cases in which a record of the pulse rate has been kept during convalescence, it has been shown that tachycardia becomes more accentuated as convalescence proceeds. This is a factor which has to be seriously considered in soldiers convalescing from bacillary dysentery under active service conditions.

E. B. Gunson (1916) noted that dyspnoea, palpitations, præcordial pain, vertigo, and exhaustion were the chief symptoms, and that the only drug beneficial for this form of cardiac distress was adrenalin subcutaneously every four hours in doses of 5-10 minims.

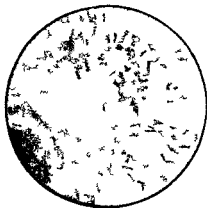
## PLATE V

### SIGMOIDOSCOPIC APPEARANCES

- A Amœbic Ulceration of lower rectum, giving rise to symptoms suggesting carcinoma
- B Intestinal Bilharziasis —Early stage Patches of granulation tissue containing eggs of *Bilharzia mansoni*
- C Chronic Bacillary Dysentery Pseudopolyposis.—Flexner's infection Agglutination test positive to Flexner 1 180 Great improvement on intestinal lavage
- D Acute Amœbic Dysentery —Active ulceration of mucosa with blood and mucus exudate
- E Acute Bacillary Dysentery.—Shiga's bacillus isolated General œdema of mucosa, spasm, submucous hæmorrhages Early healing stage
- F Amœbic Dysentery.—Chronic stage, showing "pitting" of mucous membrane



A



B



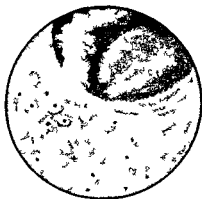
C



D



E



F

**Peritonitis**—Acute perforation of the large intestine has been recorded by N H Fairley recently in three cases in the Middle East. Localized subacute peritoneal effusions with adhesions in the right iliac fossa have also been described in the chronic form. Massive serous peritoneal effusions have also been observed in toxic cases not responding to treatment.

**Post-dysenteric ascites**—J W D Megaw and G C Maitra thought that the ascites which is so commonly found in India in association with conditions of the liver is a sequel to repeated infection. Whenever bacillary dysentery is improperly treated the dysenteric toxins pass through the intestinal walls and give rise to an irritative peritonitis which is followed by fibrosis of the peritoneum with resulting ascites.

Ascites is more likely to occur amongst patients who continue to be carriers among such cases therefore agglutinins in the serum are more likely to persist than among an average series of recovered bacillary dysentery.

**Other diseases**—Other infections of the colon such as amoebiasis may follow on a bacillary attack. Tuberculosis of the large bowel has also to be considered as well as sprue in Eastern countries and that particularly distressing complaint mucous colitis. These sequelæ will be dealt with under their appropriate headings.



## CHAPTER VIII

### THE BACILLARY DYSENTERIES (*continued*): DIAGNOSIS

It has frequently been emphasized that in bacillary dysentery it is unwise entirely to rely on a clinical diagnosis. The acute and fulminating types of the disease are obvious, but in less marked forms difficulties arise. In making a laboratory diagnosis it is necessary that the pathologist should have had the benefit of considerable experience of this highly specialized work, for bacillary dysentery frequently occurs as a terminal infection in chronic wasting diseases such as pellagra, phthisis, kala azar, bilharziasis, amœbic dysentery and scurvy. Long sustained pyrexia may be due to superimposed paratyphoid infection. In chronic cases, persistent pyrexia and frequent rigors may be due to *B. coli* septicæmia or malaria. Malaria in dysentery is a serious complication, specially apt to appear because dysentery in a malarial subject may light up a smouldering infection. On the other hand, it may co-exist with primary subtertian malaria, in which case it is just as important to treat the latter as the former. Pneumonia, either of the lobar or broncho-pneumonic type, is a frequent terminal event in the more chronic form.

#### DIAGNOSIS BY SIGMOIDOSCOPY

It is seldom necessary to use the sigmoidoscope in making a diagnosis of bacillary dysentery in the early and acute stages of the disease, and it is doubtful whether its use is always justifiable, since the pain of introducing the instrument may be acute, and damage may result, whereas in amœbic and bilharzial dysentery instrumentation is both painless and harmless. The bowel wall is rigid and is therefore with difficulty dilated sufficiently to permit the instrument to pass far up, generally, however, this is quite unnecessary, as a glimpse of the rectal mucosa will enable a diagnosis of bacillary dysentery to be made with certainty.

The appearances at the early and acute stages, which have been described so ably by A. G. Biggam (1930), resemble very closely those described in the account which has already been given of the pathology of the bowel and are very characteristic.

The mucosa in the early stages of most acute types of bacillary dysentery, when coagulation necrosis has developed, has a greyish-green necrotic appearance with hæmorrhagic areas, and indicates grave prognosis. If the bowel is re-examined a few days later, ulceration may

be observed with sloughing of the necrotic mucosa. The patient usually, at this stage shows evident signs of toxic absorption.

In acute bacillary dysentery of a milder type (caused by Flexner bacilli) the mucosa is of a strawberry red tint with diffuse inflammation and hyperæmia bleeding when traumatized (Plate V A). The bowel usually contains much blood stained mucus often adhering to the mucosa and the superficial necrotic mucous membrane may be visualized as a thin greyish layer exposing a red raw and bleeding surface when removed. The bowel wall at this stage is usually rigid and inelastic.

When cases are repeatedly examined exfoliation of the superficial necrosis can be seen the bowel gradually resuming its normal appearance.



Fig 13—Sigmoidoscopic appearances of chronic bacillary dysentery (left) and amoebic dysentery (right)

In chronic bacillary dysentery the changes involve the whole mucosa, which is covered with granulation tissue. There is rigidity of the bowel wall with some stenosis. Amoebic dysentery shows characteristic y-shaped ulcers and submucous hæmorrhages. The intervening mucous membrane appears normal.

ance. Much viscid mucus is secreted by the bowel during the healing process.

In *contalescent bacillary dysentery* the mucous membrane is nodular rose pink or bluish red and cedematous. Numerous red blotches are interspersed caused by submucous hæmorrhages. The walls of the bowel are rigid and inelastic and the natural folding is absent. The mucosa is readily traumatized and the lumen filled with blood stained mucus.

In the *subacute stages* the bowel surface is covered with granulation tissue in irregular patches these representing areas from which the necrotic mucosa has been removed.

In *chronic bacillary dysentery* the appearances are quite unlike those of the acute form. The bowel wall has lost its elasticity being rigid and indurated. The examination is usually painful and the granular mucosa bleeds readily (Fig 19). Scrapings reveal numerous

pus and macrophage cells. The exact appearance of the bowel varies in different stages, sometimes a pseudo polypoid condition is simulated by the heaping up of exuberant granulation tissue (Plate V, B) sometimes fibrosis of the bowel wall may result in partial stenosis or fibrotic scarring. The patulous condition of the anus and atrophic appearance of the skin surrounding the anal margin, together with the wasting of the gluteal and perineal muscles, afford a considerable amount of additional evidence in diagnosis.

H. J. Smyly (1930) has emphasized a point which the author has often observed, namely, that there is in milder forms of chronic bacillary



P H M B

Fig 14 — Sigmoidoscopic appearance of *Melanosis coli* showing pigmentation of colon sometimes found as a sequel to chronic bacillary dysentery

dysentery a hyperplasia sufficient to obscure the small blood vessels which are normally visible.

Some of Smyly's cases presented ulcers in the rectum or sigmoid or both. The commonest type is a very shallow ulcer the margin of which is sharply defined and ranging in size from one millimetre or less to over a centimetre. The base is usually covered with pus, which is easily swabbed away, exposing red granulation tissue. Another type of ulcer resembles a crater umbilication or a well defined papule. By cultures from the surface of these ulcers taken with a toothpick swab, a growth of *Shiga's bacillus* may be obtained.

A striking appearance sometimes obtained in chronic bacillary dysentery, especially in the rectum, is a tessellated pattern on a red

mucosa, white granulations appearing as a delicate network, or more widely spaced

*Melanosis coli*—*Melanosis coli* is a curious condition of melanin pigmentation of the rectum and sigmoid, the nature of which is obscure. The author has seen this in three patients who had suffered from bacillary dysentery and consequent diarrhoea over a long period (Fig 14)

Attention was originally drawn to pigmentation of the colon in dysenteries by A. L. Gregg (1923) and was attributed by him to the excessive bismuth. A. F. Hurst (1937), who has written an exhaustive account of this subject, believes the pigmentation to be the result of artificial diarrhoea produced by aperients. Metastasis of pigmentation to the submucosa and mesocolic lymph glands may occur in the more advanced cases (W. M. Stewart and E. M. Hickman). H. L. Bockus, J. H. Willard and J. Bank (1933) have discovered no fewer than forty-one cases diagnosed by sigmoidoscopy. They believe, apparently on substantial grounds, that it is due to anthracene compounds in the laxatives when used over long periods, and they have found that these aperients contain resinous substances and some pigment matter which is intimately associated with active aperient principles. The deposition of this pigment in the mucosa produces melanosis.

#### X RAYS IN DIAGNOSIS

A barium enema is of little assistance in the acute stage of bacillary dysentery as an aid to diagnosis, its chief use is in the chronic stage. There the appearances obtained are those of a subacute colitis and are indistinguishable from similar appearances in chronic ulcerative colitis (Plate I, p. 42)

#### LABORATORY DIAGNOSIS

In hardly any other disease is it so essential that attention should be given to details of laboratory technique, since the symptoms of bacillary dysentery may be simulated by so many other causes of intestinal ulceration that the final diagnosis must always depend upon the pathologist, and since it is essential, in the interests of the patient, that appropriate treatment should be given at the earliest possible moment.

**Direct microscopic examination**—A provisional diagnosis of bacillary dysentery can be made by examination of the cellular exudation, and for this two conditions are absolutely necessary: (1) that the specimen has been freshly passed, and (2) that it is passed early in the course of the disease. The stool should be collected in a bed pan and brought direct to the laboratory.

The selection of a portion of the stool suitable for microscopic examination or culture should be made by the pathologist. It must be emphasized that, in both the bacillary and the amebic form, all diagnostic features may disappear after a lapse of from four to six hours, and this is especially likely under tropical or subtropical conditions. So

important is the collection of suitable material that some pathologists now prefer to obtain the blood and mucus direct by the rectal swab method (see p 70). However obtained, a portion of the blood-stained mucus should be placed by means of a platinum loop on a clean glass slide, covered with a cover slip, and examined directly with a  $\frac{1}{4}$  in lens and a low ocular ( $\times 2$ ). (It is a mistake to use a lens of too high power for the preliminary examination.) A mechanical stage is necessary.

**Cellular exudate**—The most characteristic feature of the bacillary dysentery stool under the microscope is the very large proportion of polymorphonuclear leucocytes. Red blood corpuscles, too, are very numerous and, excluding these, pus cells constitute quite 95 per cent of the exudate. It has been noted by J G Willmore, C H Shearman (1918), and others, that these polymorph cells possess distinctive ringed nuclei, due to the accumulation of chromatin on the periphery of the nucleus, they have been appropriately termed "ghost cells".

**Macrophage cells**—In addition to the polymorphonuclears, a much larger cell which seems to be characteristic of bacillary dysentery occurs at an early stage. The appearance of these cells in the stool and their characteristic refractivity have given rise to confusion in diagnosis, so that it is permissible to emphasize their importance. The macrophage (histiocyte) is a cell usually 10–45  $\mu$  in diameter, apparently derived from capillary endothelium (Fig 11 p 55) constituting about 2 per cent of the cellular exudate. It may be round, oval or even bilobed. In its cytoplasm it contains vacuoles and granules of various kinds, fat globules, and sometimes even ingested red cells, or leucocytes. Those globules of greenish colour, consist of chromatin due to the destruction of the nucleus and others consist of fat due to the protoplasmic degeneration which may be appropriately demonstrated by Sudan III stain. In their general appearance and on account of their propensity to ingest red blood corpuscles and other objects these cells have frequently been mistaken for *Entamoeba histolytica*. They are however, defunct and therefore non motile and, to the practised eye, the ground glass appearance of the protoplasm differs strikingly from that of the clear, greenish, refractile endoplasm of the amoeba. Some of the macrophage cells are much smaller—about 10  $\mu$  in diameter—and these have been described by various workers as 'refractile cells,' but by appropriate staining, the details of their endothelial nucleus can be distinguished. (Plate VI)

In addition columnar epithelial cells from the mucosa may be seen, as well as mononuclear leucocytes and lymphocytes. Eosinophils are rarely encountered.

**Historical account of cytodiagnosis**—The making of a preliminary diagnosis in dysentery by a study of the cellular exudate has been given the dignity of a special term 'cytodiagnosis' while A Alexeeff has named the composite picture a 'pyrogram'. Jurgens originally noted and described these cells (macrophages) in the stools of bacillary dysentery and drew

TABLE VI

Differentiation of Bacillary Dysentery and Amœbic Dysentery Stools by the Cellular Exudate

	ACUTE BACILLARY DYSENTERY	ACUTE AMŒBIC DYSENTERY
<i>Red cells</i>	Numerous and scattered throughout preparation	Numerous, occur in clumps and rouleaux
<i>Polymorphonuclears</i>	Numerous with clear cut ring nuclei	Undamaged cells extremely scarce, those which occur have eroded margins
<i>Nuclear masses</i>	Free from cytoplasm scarce	Free from cytoplasm, very common
<i>Macrophage cells</i>	Large and numerous containing ingested red cells	Rarely seen
<i>Eosinophil cells</i>	Scarce	Numerous
<i>Epithelial cells</i>	Common, generally bile stained and disintegrated	Numerous and apparently undamaged
<i>Bacilli</i>	Extremely scarce	Motile and in large numbers
<i>Entamoeba histolytica</i>	Absent	Present

The following summarizes the relative percentages of cellular constituents of the stools in bacillary and amœbic dysentery —

TABLE VII (J. Anderson, 1921)

	BACILLARY DYSENTERY	AMŒBIC DYSENTERY
Polymorphonuclears	90.7 per cent	7.5 per cent
Mononuclears	1.61 " "	0.7 " "
Lymphocytes	2.8 " "	2.5 " "
Eosinophils	0.01 " "	3.2 " "
Macrophage cells	1.8 " "	0 " "
Epithelial cells	1.48 " "	1.3 " "
Plasma cells	1.61 " "	1.8 " "
Nuclear masses	0 " "	83 " "

attention to their superficial resemblance to amoebae and the likelihood of the pathologists mistaking them for these protozoa especially in sections

The author (1912) in his work on dysentery in Fiji, once more called attention to these cells, figured them, emphasizing their distinctive characters especially in the early stages of a bacillary infection and described their appearance in sections of the bowel. In addition, he consistently employed cytodagnosis in the laboratory diagnosis of bacillary dysentery during the 1914-18 War.

This subject assumed greater importance during the epidemics of dysentery in Gallipoli in 1915, mainly because of the *imprimatur* conveyed to it by the work of G. B. Barlett (1917) in his report to the War Office. In this paper it became apparent that macrophage cells (histiocytes) had been confused with stages in the life history of *Entamoeba histolytica*. The question was pursued by the author in collaboration with J. G. Willmore (1918), and they were able to trace in microscopic sections the derivation of the macrophage cells from proliferation of endothelial cells (Fig 11, p. 55).

Almost at the same time H. M. Lynch (1917) described them as varying in size from 25-45  $\mu$ , and as being non motile, with densely granular cytoplasm and a large ring form nucleus. He rightly considered them to be endothelial phagocytes and similar to large wandering body cells.

J. G. Willmore and C. H. Shearman (1918), in an exhaustive paper, still further emphasized the importance of cytodagnosis in the differential diagnosis of the dysenteries, and drew up a categorical statement upon the cell picture of amoebic as contrasted to that of bacillary disease.

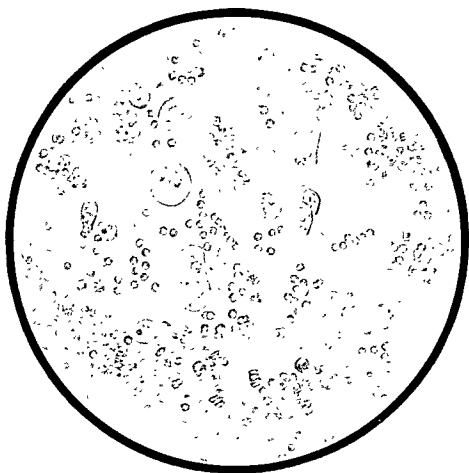
J. Anderson (1921) working in the author's laboratory in Palestine made differential cell counts of the cellular exudate in the two diseases. J. G. Thomson and A. Robertson (1921) gave a series of figures illustrating the morphology of the inflammatory cells in the exudate.

This was followed in 1924 by a monograph by F. G. Haughwout in which the importance of cytodagnosis was perhaps over emphasized. He concluded that in bacillary dysentery the cellular exudate is characteristic of that condition and of no other intestinal disorder. The phagocytic endothelial cells and the annular degeneration of the nuclei of the polymorphonuclear pus cells are considered pathognomonic; on the other hand, he held that ghost cells and endothelial cells are absent in acute amoebic dysentery and in balantidiasis.

Finally A. Alexeieff (1927) repeated with elaborate care the researches already outlined and reached much the same conclusion. He emphasized the importance of the macrophage cells (plasmophages) which are found in abundance in the mesenteric glands of acute bacillary dysentery cases as well as in the exudate.

*The proportion of Shiga to Flexner bacilli isolated from the stools during the course of an epidemic*—It has frequently been pointed out that at the commencement of an acute epidemic typical dysentery bacilli can be isolated from the faeces, but as the epidemic progresses atypical forms of dysentery bacilli make their appearance.

In Palestine during the 1914-18 War the author (1919) constructed a graph (Chart 1) showing the proportions of bacilli isolated from the dysenteric faeces received at his laboratory together with the percentage of Shiga and Flexner bacilli obtained during consecutive months. It will be seen that the number of Shiga and Flexner bacilli run roughly parallel with one another.



*P. H. Manson Bahr del*

**MICROSCOPIC APPEARANCE OF CELLULAR EXUDATE  
IN ACUTE BACILLARY DYSENTERY (Shiga infection)**

Fresh preparation. Shows macrophage cells (histiocytes) with  
ingested red blood-corpuscles, intestinal epithelium and polymor-  
phonuclear leucocytes.

**PLATE VI**



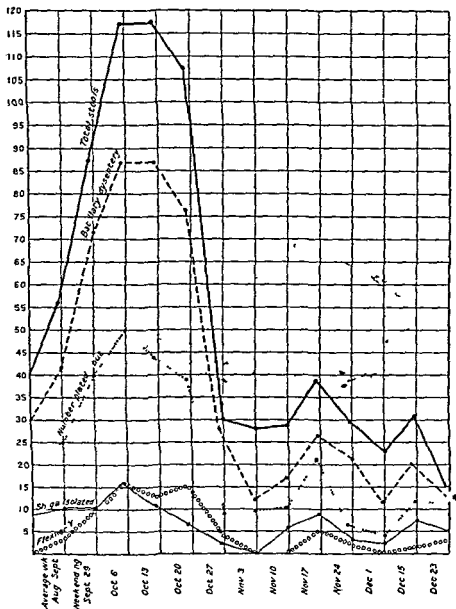


Chart 1—Illustrating the proportions of positive stool cultures obtained under war conditions to the number of "dysentery" faeces examined (1917). \* Denotes the number diagnosed bacillary dysentery on the cellular exudate

(Manson Bahr Jour R Army Med Cps., Aug., 1919)

The total number of stools examined during this period was 837, and in 664 of these the specific cause could be ascertained —

(1) 6 (0·9 per cent) were associated with *Giardia intestinalis*, (2) 11 (1·6 per cent) with flagellates—*Trichomonas* or *Chilomastix*, (3) 7 (1·05 per cent) with *F. histolytica*, (4) 633 (95·3 per cent) were diagnosed in the cellular exudate as *bacillary dysentery*, (5) 342 (51 per cent) were plated out, (6) in 201 (59·1 per cent) dysentery bacilli were isolated, (7) in 114 (33·5 per cent) *Shiga* s bacillus, and (8) in 87 (25·4 per cent) *Flexner* Y bacillus.

In any large epidemic, bacilli of more than one type are found and a pure *Shiga* or a pure *Flexner* epidemic appears to be a rarity. In Salonica, L. Dudgeon (1918) obtained the following figures —

	Cases	Percentage
Shiga B	335	38·3
Flexner B	503	57·3
Other Types	30	4·1

D. Graham and his collaborators (1918) obtained much the same figures in 2,500 cases.

**Examination of material obtained by sigmoidoscopy.**—In the subacute type of bacillary dysentery the routine use of the sigmoidoscope enables the investigator to discover ulcerated areas and to obtain cultures, it has been abundantly confirmed that these areas afford a suitable nidus for the causal bacilli. In the acute stage of the disease sigmoidoscopy cannot be used without employing a general anæsthetic, while in many of the chronic cases no suitable ulcerations can be discovered in the rectum or those parts of the pelvic colon which can be reached by the instrument.

**Examination of material obtained by rectal swabs.**—During the 1914-18 War, on the Western Front, this method was extensively used for obtaining suitable material for culture from the lower rectum, and the results are more satisfactory than those obtained by culturing freshly passed motions. Recent experience has also borne out this claim (p. 70). (See also Appendix II, p. 557.)

Ziemann's tube consists of a glass tube 28 cm long by 2 cm in diameter, the walls of which are 1·5 mm thick. Situated 9 cm above the lower end, which is closed as in a test tube, is a circular opening, 1·5 cm in diameter. When it is desired to obtain a sample of the intestinal contents, the rounded end of the tube is introduced into the rectum and pushed gently upwards with a rotatory movement, with the result that some of the mucus or fæces passes into the lumen through the lateral opening. On withdrawing the tube a sample of the contents can be removed through the lateral aperture. The apparatus is then washed and sterilized.

The reader is referred to the Appendix, p. 550 for further details.

of the technique of isolation of the organisms and the types of media employed

**Methods employed in chronic bacillary dysentery**—In the author's series of 107 cases of chronic bacillary dysentery in the Hospital for Tropical Diseases, London, during the years 1920-87, the great majority were diagnosed by sigmoidoscopic appearances, 21 were diagnosed by the agglutination test, 12 by sigmoidoscopy as well as by the agglutination test, but only 8 by actual isolation of Flexner's bacillus from the faeces

**Serological diagnosis**—It cannot be sufficiently emphasized that accurate diagnosis is of paramount importance in the differentiation of the dysenteries, therefore, every means must be brought to the aid of the clinician in a particularly difficult case. It is a matter of considerable disappointment that serological diagnosis, usually so satisfactory in the typhoid group is such a comparatively unreliable weapon in bacillary dysentery

In the first place, some normal sera have a definite action upon freshly prepared emulsions of dysentery bacilli (A. D. Gardner, 1923). It has already been emphasized that only the macroscopic method is suitable in dealing with these organisms. The best results can be obtained by using Dreyer's technique with definitely sensitive agglutinable emulsions. It is the general opinion that in Shiga infections a positive diagnosis can be accepted when the titre is as low as 1:40 but with the Flexner group agglutination should take place in a dilution of 1:100. The difficulty of obtaining positive results in certain circumstances arises not so much with Shiga as with Flexner cases. The reason for the lack of a substantial reaction in the latter is to be found, probably, in the numerous serological races which have been described for that organism, and it is therefore necessary to use a homologous suspension for agglutination.

There are fallacies in the use of the agglutination test in this connexion which may be stated as follows. It is difficult to accept a negative test as being of value unless it is made after the eleventh day of the disease. The agglutinins appear generally about the seventh and reach their maximum about the twenty first day and then show a rapid decline. A previous attack of bacillary dysentery may have to be taken into account, as residual agglutinins may persist in the serum for a considerable time—it has been stated that these can be demonstrated after as long an interval as three and a half years. The limitations of this test, therefore, are very obvious, and in those acute cases in which a rapid diagnosis is very urgent it is, unfortunately, of little value.

The agglutination test as an aid to diagnosis was originally investigated by the author in his work on dysentery in Fiji in 1912. The microscopic test alone was utilized, with culture isolated from actual dysentery cases under treatment. The sera of 112 cases were tested. A positive agglutination

with Shiga s bacillus was noted in 74.1 per cent in dilutions of 1:100-1:200 and in isolated instances as high as 1:500. Similarly in a series of fifty six cases of Flexner infection a positive agglutination was noted in 60 per cent in dilutions of 1:100-1:200 and in eight instances as high as 1:500.

I. Dudgeon (1918) investigated the agglutination reaction of bacillary dysentery during the seasonal epidemics in Salonica in 1916, 1917 and 1918. As a result of this careful work he concluded that with standardized bacillary emulsions by the macroscopic method (1) a reaction of 1:40 is positive indication of a Shiga infection (2) a reaction of 1:25 is strongly suggestive of a Shiga infection and in such cases the blood should be examined a week later and (3) Shiga cases may show a high Flexner agglutinin content in the serum.

The highest agglutinin titres were encountered during the second and third weeks of the disease. No agglutinins were found before the fourth day. In a Flexner infection it is necessary, according to modern knowledge, to employ at least five separate serological stains of Flexner antigens for the results obtained with one differ from those obtained with another.

The conclusions arrived at are that the agglutination test is a valuable and reliable method of diagnosis of Shiga dysentery, but the diagnosis of Flexner dysentery by agglutination is associated with considerable difficulties because of the high Flexner agglutinin content which may occur with a Shiga infection. Recently however, more satisfactory and consistent results have been obtained by employing a pooled antigen of the different types described by Boyd (1939) (see p. 561). He emphasizes that smooth specific cultures must be used and this applies especially to Schmitz and Sonne bacilli.

In cases of clinical dysentery (i.e. cases in which bacteriology of the faeces has given no assistance) in which the Shiga reaction is negative on the first occasion although a reaction to Flexner has been recorded it is necessary to repeat the examination seven days later with Shiga and Flexner antigens as by this time a Shiga reaction may have developed.

J. Speares and P. P. Debono (1919) have contributed to this subject by confirming that a serological diagnosis is not always possible in mild Flexner infections and that the injection of curative serum has no appreciable effect upon the specific agglutination titre. They point out that in arthritis agglutination may be of considerable diagnostic value as the joint complications may be indistinguishable from other kinds of metastatic arthritis.

The results obtained by C. P. Martin, P. Hartley and F. E. Williams (1918) are in the main in agreement with these conclusions.

V. de Lavergne, P. Melnotte and R. Debenedetti (1930) have not added anything material to the conclusions arrived at above.

For the identification of dysentery bacilli by serological methods J. S. K. Boyd (1940) has adopted the following procedure. Shiga antiserum and Schmitz antiserum permit the differentiation of the mannitol non fermenters by slide agglutination. For the mannitol fermenters anti Sonne serum containing both specific and group agglutinins for Sonne, a polyvalent serum of Andrewes Flexner types and another for types 103, P 119, 88, and 170. A practical difficulty is encountered in the latter in preparing single pool type sera with a titre of 1:250 for each type.

In chronic cases of bacillary dysentery a definite result may be obtained in Shiga infection; a titre of 1:40 or over is usually accepted. The same probably applies to Schmitz and Sonne infections if care is taken to prepare the agglutinable suspension from the type phase of the organism. In Flexner infections the problem is beset by difficulties on account of the multiplicity of strains and it is almost impossible to prepare suspensions which are free from group antigens. Furthermore, serum from normal individuals and from normal rabbits frequently contains a considerable concentration of natural agglutinins for these group antigens.

**Serological properties of dysentery stools.**—A. Davies (1922) found that dysentery agglutinins were present in dysenteric stools even when absent from the serum, especially during the first week of the illness. Either the fluid portion of the stool was pipetted off, or the blood and mucus were thoroughly shaken up with a small quantity of normal saline. The technique adopted to ascertain the presence and titre of agglutination was that of Garrow (*see* Appendix, p. 565). The method is especially valuable in Shiga infections, and in chronic cases it was found particularly helpful, the specific agglutinins being obtained from pledgets of mucus passed in the faeces.

**Examination of the blood.**—G. M. Findlay (1919) found that assistance can be obtained in differentiating bacillary from amoebic dysentery by the reactions which occur in the polymorphonuclear leucocytes—the iodine reaction and the production of nuclear pseudopodia. He considered that an accurate diagnosis of the type of dysentery can be given at an early stage of the disease. A well marked iodine reaction without the formation of nuclear pseudopodia suggests a bacillary infection; the presence of nuclear pseudopodia with absence of the iodine reaction indicates amoebiasis.

**Intradermal reactions.**—H. Brokman (1923) applied the Schick reaction to dysentery in man in the following manner.—0.1 c.c. of Shiga dysentery toxin in a dilution of 3:100 is injected under the skin, and a very considerable reaction is produced at the end of twenty-four hours. A diffuse red infiltration appears, turning blue. When the reaction is stronger, the skin becomes blue, and afterwards deep brown, while at the end of a week an ulcer may form. This reaction becomes negative after injections of antidyenteric serum.

C. Zoeller (1927) has also described a similar reaction. He uses 0.2 c.c. of a 1:100 dilution of dysenteric toxin. The specific reaction does not appear till the third or fourth day, when an ecchymotic tinge becomes pronounced and leads to the formation of a small black slough. A negative reaction indicates the presence of sufficient antitoxin to neutralize the toxin.

**Summary.**—The following is a summary of the main points in differential diagnosis.

#### DIAGNOSIS BETWEEN BACILLARY AND AMOEBIC DYSENTERY

BACILLARY DYSENTERY	AMOEBIC DYSENTERY
"Lying down dysentery."	"Walking dysentery."
Acute disease with tendency to epidemic spread.	Chronic endemic disease

## BACILLARY DYSENTERY

**Incubation period** short, seven days or even less

**Onset** Acute

**Pyrexia** Common

**Complications** No hepatitis Poly arthritis frequent, and occasionally irido cyclophitis

**Death due to** (a) exhaustion  
(b) toxæmia

**Signs** Generalized tenderness over abdomen, usually more intense over sigmoid colon

**Tenesmus** Very severe

**Emaciation** Almost invariable

**Pathology** Acute diffuse necrosis of mucous membrane of the large intestine

**Ulcers** When present, situated on free edge of folds of mucous membrane, distributed transversely to long axis of the bowel. Ulcers are usually serpiginous with ragged undermined margins, often intercommunicating. Bases consist of granulation tissue, no compensatory hypertrophy of the bowel wall. Intervening mucous membrane chronically inflamed

**Stools** Small numerous Bright red blood, gelatinous viscid, odourless, resembling red currant jelly

**Reaction** Alkaline

**Microscopic** Numerous red cells and polymorphonuclear pus cells. Macrophage inflammatory cells (histiocytes). Few bacilli visible

## AMOEBIĆ DYSENTERY

**Incubation period** in man a lengthy one—at least fourteen to ninety days, may be longer

**Onset** Insidious

**Pyrexia** Rare, unless complicated

**Complications** Hepatitis, hepatic amœbiasis, amœbic abscess

**Death due to** (a) exhaustion  
(b) perforation of the bowel  
(c) hæmorrhage  
(d) liver abscess

**Signs** Local tenderness and infiltration, mostly over sigmoid flexure, transverse colon, and cæcum

**Tenesmus** Usually not present

**Emaciation** Uncommon

**Pathology** Local lesions confined solely to large intestine, due to characteristic ulcers

**Ulcers** Bouton en chemise"—commence as small abscesses of submucosa, distributed in the long axis of the bowel. Ulcers oval, regular, flask shaped. Infection involving all coats of the bowel. Bases usually consist of dark necrotic Dyak hair sloughs. Ulcers perforate not uncommonly, compensatory hypertrophy of bowel wall. Intervening mucous membrane quite healthy

**Stools** Faeces intermingled with blood and mucus. "Sago-grain" stool, or sometimes "anchovy sauce." Copious in amount and usually very offensive

**Reaction** Acid

**Microscopic** Red cells numerous and in rouleaux. Polymorph cells much damaged with extruded nuclei. Macrophage cells absent. Large numbers of motile bacilli. Active *Entamoeba histolytica* with ingested red cells. Charcot Leyden crystals common

## BACILLARY DYSENTERY

*Blood examination* No leucocytosis except in initial stages

*Serum agglutination* Usually serum agglutinates one or other dysentery bacilli

*Therapeutic test* No reaction to emetine

*Sigmoidoscopy* Granulation tissue and rigidity of bowel wall Usually no ulcers visible

Differential diagnosis from the enteric group food poisoning cholera acute ulcerative colitis and other forms of dysentery is dealt with under their respective chapters

## AMŒBIC DYSENTERY

*Blood examination* Moderate leucocytosis

*Serum agglutination* Negative

*Therapeutic test* Almost immediate reaction to emetine

*Sigmoidoscopy* Lax and redundant mucous membrane Small ulcerations with hæmorrhagic margins

## CHAPTER IX

### THE BACILLARY DYSENTERIES (*continued*): TREATMENT

BACILLARY dysentery is a disease which in its early stages appears to be particularly amenable to treatment, so that milder cases recover spontaneously without any particular measures. In the more acute, especially in fulminating cases, prompt and energetic action is necessary, while skill and care in nursing are naturally of importance.

**General principles**—The patient should be put to bed, however mild his initial symptoms may appear. He, or she, should be warmly clad and should on no account be permitted to get out of bed to defæcate. In addition to general supervision, daily inspection of stools should be made.

**Diet.**—Special attention must be given to the dietary. Under no circumstances are solids permissible. In the more severe forms, which are attended with considerable gastric disturbance, milk is not well tolerated and, as a rule, jellies, weak beef tea, arrowroot chicken broth, or rice water are preferable. The food should be served slightly warmed and in small quantities, otherwise it is apt to cause increased peristalsis and to aggravate pain.

Whenever milk cannot be assimilated, it is advisable to give it in the citrated form or in the form of some predigested preparation such as Benger's Food. The ideal diet in severe bacillary dysentery should be definitely bland, unirritating but nourishing.

During convalescence discretion should be exercised. Under no circumstances should patients be rushed through this stage, too rapid introduction of solid food is apt to lead to sudden and profuse attacks of diarrhœa which may result in collapse. On the other hand, it is quite unnecessary to keep the patient on a dietary so low in caloric value that he is practically starved.

The following diets have been recommended by J. M. Cowan and H. Miller (1918). The chief indication for the change from one diet to the next should be the state of the tongue and the character of the stool. Fluids should be given in generous quantities especially when the diarrhœa is acute. During the diarrhœa accompanying convalescence a dry dietary should be instituted.

	<i>Diet No 1</i>
6 a.m.	Tea (10 oz.)
7.30	Albumin water (6 oz.)

<i>Diet No 2</i>
Tea (can be made with milk)
Two beaten up eggs with tea and milk



	<i>Diet No 1</i>	<i>Diet No 2</i>
9 a m	Brand's essence of beef (6 oz )	Barley water
10.30	Barley water (10 oz )	Benger's
12 noon	Beef tea (10 oz )	Beef tea, custard or rice cooked in water
1 30 p m	Albumin water (6 oz )	Jelly (2 p m )
3	Jelly	
4 30	Tea (10 oz )	Tea with rusks and biscuits
6	Chicken tea (10 oz )	Chicken tea or Bovril
8	Albumin water (10 oz ),	Benger's or arrowroot
10	Bovril (10 oz )	Brand's essence
12 midnight	Brand's essence (6 oz )	Albumin water
2 a m	Barley water (10 oz )	Bovril
4	Albumin water (10 oz )	Benger's

To either diet citrated or peptonized milk can be added, but it is badly borne when the tongue is coated. Chocolate can be added to No 2

*No 3 Diet* Add boiled or poached eggs with junket or milk food (Horlick's or Allenbury's)

*No 4 Diet* Add fresh cream, rice milk puddings, and toast

*No 5 Diet* Add fish and bread.

*No 6 Diet* Chicken diet, at first without potatoes, vegetables or porridge

*No 7 Diet* Convalescent diet

Moro's apple diet is strongly recommended by German writers (see also p 457). It consists of apple pulp, up to two pounds a day, with lemons for vitamin C and fluid by the mouth in large quantities

#### SPECIMEN CONVALESCENT DIET FOR BACILLARY DYSENTERY

*Breakfast* —

Milk ( $\frac{1}{4}$  pint)

One egg, lightly boiled

Two breakfast biscuits or rusks with butter

10 a m —

Milk ( $\frac{1}{4}$  pint)

One biscuit, or rusk

*Lunch* (1 p m) —

Steamed fish, well pounded 4 oz

Custard made of one egg and 5 oz milk.

Juice of two oranges in water

A thin slice of dry toast

*Tea* —

Milk ( $\frac{1}{4}$  pint)

Three rusks or breakfast biscuits and butter

One lightly boiled egg

*Supper* —

Scraped beef (1 oz ) mixed with Marmite, spread upon a piece of crisp toast and butter

Junket made of  $\frac{1}{4}$  pint milk

Juice of two oranges in water

10 p m —

Milk ( $\frac{1}{4}$  pint)

Allow  $1\frac{1}{2}$  oz of sugar daily

**Treatment of severe cases**—In enumerating the various methods of treatment, it is proposed to deal first with those cases which are the most severe, for in these irreparable damage is done if the disease is not recognized early and treated efficiently. When once this opportunity is missed, it is no longer possible to restore bowel function.

**General measures**—The patient must be put to bed and kept warm with hot water bottles. A warm bed jacket is advisable, and the abdomen should be protected by flannel binding or by a suitable cholera belt, these measures, besides guarding against chill, afford warmth which is of considerable comfort. The foot of the bed should be raised. The patient should, in fact, be treated on general lines, in the same way as a case of surgical shock.

In the most severe cases, where the passage of stools is almost continuous and the abdominal pain excruciating, the patient should on no account be permitted to exhaust his physical strength by straining on a bed pan. Every measure should be taken to minimize physical strain, which undoubtedly militates against a favourable outcome. In very collapsed cases incontinence both of urine and of faeces is common and it is best to pack the buttocks well with carbolyzed tow or cotton wool over a waterproof sheet which can be cleaned and changed every few hours. Great care must, of course, be exercised in keeping the patient's skin clean by means of spirit and boracic. Complete rest both mental and physical must be insisted upon, for rest itself exerts considerable influence on the bowel.

The mainstay in the treatment of these serious cases nowadays is sulphaguanidine, in conjunction with antidyenteric serum and blood transfusions.

**Aperients**—It is a well established and sane practice to commence treatment by a preliminary purge, in order to clear the large intestine of any remaining faecal contents. The aperient most suitable for this purpose is castor oil to which, in order to obviate unnecessary griping, some opium should be added as follows—

Oil ricin	$\frac{1}{2}$ oz (15 c.c.)
Tinct opu	15 minims (1 c.c.)

This should be given preferably last thing at night, and may be repeated.

For small children, liquid petroleum, e.g. Nujol, in half-drachm doses is probably preferable, and should be given every two hours while the child is awake. T. H. Gunewardene (1934) recommends Hydrolax in older children. No other purgatives or intestinal antiseptics are required. It is suggested that these preparations act like natural mucus and thus protect the bowel.

R. W. Burkitt (1921), of Nairobi, recommended Turkey rhubarb in doses of half a teaspoonful every two hours until it is possible to verify the appearance of the drug in the stools. For children 5 grains of rhubarb are more suitable, but some think that on the whole castor oil is of more value. H. C. Brown (1923) has shown that there is no reason

to suspect any specific action on the part of the rhubarb, as extracts do not inhibit the growth of the dysentery bacillus

**Saline treatment** — Following the preliminary aperient, routine treatment with saline aperients should be begun. This is a time honoured method and one which has received almost universal commendation, especially from Indian physicians and wherever it is necessary to treat bacillary dysentery on a large scale. Most clinicians appear to prefer sodium sulphate to the magnesium salts. It may be given in the following prescription —

Sod sulph	60 gr (4 grm)
Acid sulph dil	15 min (1 c c)
Tinct zingib	5 min (0.3 c c)
Aq menth pip	$\frac{1}{2}$ oz (15 c c)

It is a well established rule that a dose of this mixture should be administered every two hours for the first twenty four, and thereafter every four hours till the stools become *faculent*, subsequently it is customary to give it three times a day, but some prefer to give it even more frequently, for instance, every hour for the first forty eight hours. The author prefers the more moderate course.

It is only right to add that some prefer other purgatives, e.g., 2 oz of castor oil on the first day, and one drachm hourly during the daytime on the second or third day. A. J. Boase (1925) and T. B. Welch and C. J. Mascarenhas (1924) believe that the castor oil treatment is more efficient than the older fashioned salines. They consider that repeated small doses keep up gentle and continuous peristaltic action, so that the contents of the small intestine are hurried on and toxic absorption is reduced to a minimum. The castor oil treated series showed a greatly reduced death rate (2.77 per cent as against 8.8 per cent in the saline treated group) and curtailment of duration of symptoms, while the relapse rate was also considerably smaller.

**Drugs in bacillary dysentery** — *Sulphonamides* — It is pleasant to record that important advances have been made in the treatment of the bacillary dysenteries. The present position appears to be that these efficient remedies suffice to cure cases of average severity, but do not exclude the employment of blood transfusion, dietetic and other measures directed towards supporting resistance, but it seems more than probable that the therapeutic value of antidyenteric serum save in exceptional circumstances, may henceforward be discounted.

By 1938 sulphonamide compounds had given highly promising results in the laboratory, inhibiting and preventing growth of Flexner and Sonne bacilli. Since the outbreak of the present war opportunities have been provided for testing these compounds in the field and in the Near East.

V. Gurlitzer in Switzerland employed prontosil, 0.5 grm thrice daily for three days, from the fourth to seventh days 1 grm of prontosil daily combined with charcoal and 10 minims of tincture of opium whenever indicated. Prontosil was found specially effective in Shiga infections.

R. Reitler and K. Marberg (1941) in an outbreak in Palestine, obtained remarkably good results with sulphapyridine. They gave 1 grm doses with sodium bicarbonate (to counteract nausea), four times daily for 2-4 days.

The pyrexia was almost immediately reduced and motions became formed in 48 hours. These were Flexner and Sonne infections.

Bell in England had the opportunity of treating a small outbreak of Flexner and Sonne dysentery, with excellent results by sulphapyridine in doses of 3 gm daily, with a total of 5 gm\*. Symptoms cleared up entirely within 36-72 hours. The effect on pyrexia was immediate and the patients became constipated two to three days after the disappearance of blood and mucus from the stools. No symptoms of intolerance were shown. A very important fact was that sulphonamide banished the carrier state.

**Sulphaguanidine** (sulphanilylguanidine)—E. K. Marshall, A. C. Bratton, H. J. White and J. I. Litchfield have improved this form of therapy by the introduction of a new compound—sulphaguanidine. The main virtues of this modification lie in its water solubility, therapeutic activity and the fact that it is poorly absorbed from the intestinal tract, it thus differs from the so called intestinal antiseptics which have depended so far upon low water solubility to avoid intestinal absorption. The fundamental principle aims at a high concentration of the drug in the intestinal contents, contrasted with low concentration in blood and tissues. Sulphaguanidine is highly bactericidal and has a water solubility of 220 mgm per 100 c.c. The solution is practically tasteless. It appears to be more readily absorbed from the small intestine than from the large. Material obtained from ileostomy shows that the drug is concentrated in the intestinal contents in concentration greater than 200 mg per cent and saturation of the faeces is thereby assured.

Clinical results obtained in a preliminary series of 17 Flexner and Sonne infections in children were almost wholly favourable judging by the rapid defervescence, the formation of the stools and the disappearance of causative bacilli. No definite toxic results were observed. The following dosage programme is recommended—Initial dose 0.1 gm per kilo by mouth. Maintenance dose of 0.05 gm per kilo every four hours until the number of stools is less than four, subsequently, 0.1 gm per kilo every eight hours for at least three days. The finely powdered drug is given in milk or water.

G. M. Lyon has published a more extended account of his personal experience in twenty three cases of acute bacillary dysentery with adequate controls. The patients were mostly children but ranged in age from two months to 75 years.

The above comprises the medical literature which has appeared on this important subject up to date but sulphaguanidine is being extensively employed in military practice in the Middle East and the practical results obtained have been extremely satisfactory.

*The latest report on war experience in the Near East is from N. H. Fairley and J. S. K. Boyd.* It is to the effect that sulphaguanidine is most efficacious in Shiga infections of which 96 were analysed. The outstanding features are—the increased feeling of well being within 24-48 hours of administration, rapid relief of abdominal pain and

\* i.e. the drug is given for 1½ days only.

tenesmus, decrease or disappearance of abdominal symptoms, fall in temperature and pulse rate, together with a remarkable reduction in the number of stools. As a rule, within 5-6 days the bowels act once or twice daily, and blood disappears rapidly from the faeces. In the acute cases the average dose is 20 grm per diem, with an aggregate of some 135 grm for each case. For mild acute cases of Shiga infection the recommended dose for adults is 20 grm each day for the first two days, and 10 grm each day for the next three days. In individuals who are not ill, but from whom true dysentery bacilli can be recovered, the doses suggested are 18 grm in the first 24 hours, administered in 6 grm doses three times a day after meals, subsequently 3 grm three times a day for five days.

The earlier that treatment with sulphaguanidine is commenced, the less extensive is the damage to the colon and the more rapid the recovery. The most dramatic cures were found in acute cases treated within 24-36 hours of the onset. In the fatal cases, where failure appeared to have occurred, some complicating factor was proved to be present.

The action of sulphaguanidine is either bacteriostatic or bactericidal and leads to immediate decrease in toxin production, but appears to have no effect on dysentery exotoxin absorbed into the blood. These writers consider that the best results will be obtained by combining sulphaguanidine and Shiga antitoxin (antidysenteric serum) in fulminating Shiga dysentery in which it is imperative that circulating toxin should be rapidly neutralized. No severe toxic manifestations were noted, exceptionally there was a transient papular eruption. The toxic nephrosis (toxæmic nephritis), which has been found not infrequently complicating bacillary dysentery, has no relation to administration of the drug. It is said to be less efficacious in Sonne infections, but a new compound of the same series, sulphamethazine is reported more satisfactory.

D E W Anderson and R Cruickshank (1941) have summarized their experiences in 41 adult cases of Flexner dysentery in England and have obtained beneficial results, particularly in the more severe infections. A series of 55 cases in the same epidemic served as controls. A dosage of 9 grm daily for two days followed by 4 grm for two to five days was therapeutically effective. Still larger doses were safely tolerated, and even advisable, in severe infections. Prompt treatment with this drug in the acute stage of infection prevented the convalescent carrier state which was found in about one half the control untreated group. Toxic effects were not observed, but when the drug was given too concentrated, crystalline deposits occurred in the urine, necessitating adequate fluid intake if irritation of the urinary tract was to be avoided.

*Medicinal charcoal*, a tablespoonful three times daily, is useful as an intestinal disinfectant, and *carbo medicinalis* "Merck" is strongly recommended by Weiss (1927).

*Isogel*, a granular preparation of agar produced by Allen and Hanbury,

given in teaspoonful doses, is useful in solidifying the stools and checking the diarrhoea.

The author is strongly opposed to the use of *opium* as a routine measure in the treatment of dysentery, and preparations of opium, morphia, laudanum and chlorodyne, however comforting, must not be looked upon as a means of cure. The idea of putting the bowel "in splints" by means of opium demonstrates a lamentable ignorance or failure to appreciate the true pathology of the disease. If doses of opium are consistently given it may ease the continuous diarrhoea, but an exacerbation of toxic symptoms almost certainly ensues. Its use should be confined to procuring rest and sleep and to enabling a patient to withstand the fatigue and trials of a long journey as for instance, evacuation from a field ambulance in war time. Morphia should be given preferably by the hypodermic route, but in doses no larger than  $\frac{1}{4}$  gr (0.016 grm.)

The routine administration of *bismuth* has many adherents and it is given in drachm doses (3.8 grm.) every three hours during the acute stage. The carbonate or salicylate should be used, not the subnitrate which in such heroic doses may liberate poisonous compounds. Wartime physicians believed that this drug exerted a beneficial action in acute cases and they considered that the blackening of the stools consequent on its administration indicated a favourable outlook but if this blackening did not occur the prognosis was bad indeed since it meant that paralytic distention of the small intestine had taken place.

In Germany and Austria the exhibition of *kaolin* with the addition of animal charcoal in doses of three tablespoonfuls of each is much used and is well spoken of. It is probably better to give the preparations known as colloidal kaolin or Kavlenol.

Some patients do not tolerate saline aperients well, and in these *calomel* ( $\frac{1}{2}$  gr every hour for twelve hours on three consecutive days) is used.

**Intestinal disinfectants** — These have been much used in the treatment of dysentery, but their curative effect is probably small. Salol in doses of 5-15 gr (0.3 to 1 grm.) in cachets or in suspension has been tried and the author has used *elylin* in 2 min. cachets in quantities of twenty to thirty a day. R. S. Martodiwirio and M. U. Thierfelder (1932) recommend *rivanol* in the mass treatment of bacillary dysentery. In fact they consider that serious epidemics may be cut short by rivanol treatment. Adults should receive 50 mgm in pills three times daily and children correspondingly smaller doses. Rivanol has the merit of being cheap and not accompanied by any untoward effects or idiosyncrasies.

**Preparation of antidysenteric serum** — In the British Pharmacopœia for 1932 it is laid down that the potency of antidysenteric serum shall be determined by comparing the dose of it necessary to protect mice against the lethal effect of dysentery toxin with the dose of a standard preparation of antidysentery serum (Shiga) necessary to give the same protection. The standard preparation is a quantity of dried serum obtained from horses immunized against *Bacillus dysenteriae* (Shiga).

**Storage**—Antidysenteric serum (Shiga) should be kept at as low a temperature above its freezing point as possible. It should be stored in glass phials, preferably not in bottles with rubber caps, as these, especially in the tropics, are very apt to be contaminated. In the tropics, too, the serum must be kept on ice, because there is no doubt that continuous heat causes a considerable diminution in antigenic power.

**Principles underlying serum-therapy**—The first serious attempts to produce an efficient antitoxin in bacillary dysentery were made by C. Todd in 1904 in London and L. Rosenthal (1903-1904) in Moscow. They showed quite independently of one another that the soluble toxin contained in cultures of *Shiga's bacillus* was capable on injection into animals of giving rise to a neutralizing antitoxin. Thus union of toxin and antitoxin in antidysenteric serum is said by Pfeiffer and Ungermann (1909) and by Kolle and others (1924) to conform to the law of multiple proportions.

There has been some doubt about the real antitoxic powers of this serum because complete neutralization only occurs when toxin and serum are intimately mixed, but from the work of Kraus and Dörr (1905) there seems to be little doubt that the serum contains true specific antitoxin.

Antidysenteric serum is produced by the intravenous injection of horses first with heat-killed and later with living bacilli (S. Flexner 1916). More recently dysentery anatoxin has been used for its production (Dumas and others 1926).

The titration of this serum is best carried out by intravenous inoculation in mice.

R. A. O'Brien and B. F. Runge (1925) have suggested that the limit of antitoxin should be that amount of serum which will neutralize the test dose—0.2 mgm. of a standard toxin—the test dose being approximately ten lethal doses for the mouse. An improved method was described by A. V. Blake and C. C. Okell (1929). They concluded that the serum treatment reduced the mortality by two-thirds.

On account of the difficulty—almost in fact impossibility—of ascertaining rapidly which particular dysentery bacillus is responsible for the acute attack, it has been the practice to use a polyvalent anti-dysenteric serum. For the preparation of these sera, horses are immunized against *Shiga's bacillus* and various Flexner strains. The difficulty in the production of suitable antidysenteric sera lies in the fact that such sera contain but small amounts of efficient *Shiga* immune bodies. It is apparently much easier to produce an efficient anti-Flexner serum but, as the most acute cases of bacillary dysentery are usually due to an infection with *Shiga's bacillus*, it is naturally of the greatest importance that the clinician should have at his disposal an efficient *Shiga* serum. Such sera are produced by the *Lister Institute* by Mulford of Philadelphia, by the *Rockefeller Institute* by Burroughs Wellcome and by the *Berne Institute*.

**Serum-therapy**—No consensus of opinion can be obtained on which class of case should receive anti-serum treatment. In the author's opinion care should be exercised in the selection of cases and the indications should be based upon (a) definite signs of toxic absorption, (b) stools numbering more than twelve in the twenty-four hours and containing a high proportion of blood, (c) a small rapid pulse and

definite pyrexia, (d) mild cases in which the acute stage, with bloody stools, tenesmus and abdominal pain, persists longer than three to four days and shows no signs of subsiding (Schittenhelm, 1918)

There are three routes by which the serum may be given (1) subcutaneous, (2) intramuscular, and (3) intravenous. Whichever route is selected, it is necessary to observe strict aseptic precautions. In every case the serum should be heated to body temperature by being placed in a vessel of water at a temperature of 110° F (43.3° C) for fifteen minutes.

W. E. Waller (1919), in Mesopotamia, and B. G. Klein (1919), in France, treated over 1,800 cases by subcutaneous injections of Lister Institute polyvalent serum. Large amounts in doses of 120–140 c.c. were found most beneficial. This amount of serum can be given in three injections at eight hour intervals. From the seventh day of the disease onwards the serum has less effect, by this time, usually, either the patient is doomed to die, or the stage of recovery has set in.

By the intramuscular method large amounts of serum were given without causing much local disturbance. The sites chosen were the glutei muscles or the adductor group in the thigh, where the tissues can accommodate large quantities of fluid. Intravenous injection into the median basilic vein in doses of 60–80 c.c. has been employed in very acute or fulminating cases. In collapsed patients it may well be diluted with 100–200 c.c. of saline solution containing 5 per cent glucose.

P. J. Lantin (1921) reported favourably on a method practised in the Philippine General Hospital, of injecting antidysenteric serum by the rectum. The serum is introduced through a funnel and a long rubber tube, with the patient in the knee elbow position. A preliminary cleansing enema of 15 per cent sodium bicarbonate is followed by a sedative enema of 60 c.c. of starch solution, with fifteen drops of laudanum. A high enema of serum, 30–80 c.c., should be given half an hour later. Lantin believes that a combined method of intramuscular and rectal injection in acute cases offers the best chance of success. W. Wilcox inclined towards this method as avoiding the dangers of serum reactions.

**Monovalent anti-Shiga serum**—Much of our information on the therapeutic effects of anti-dysenteric serum was derived from experiences in the War of 1914–1918 when a polyvalent serum was employed. Since that time, however, great improvements in the preparation, refining and concentration especially of anti-Shiga serum, have been effected. As issued to the Army in the present emergency it contains 50,000 international units in a volume of less than 10 c.c. Between 50,000 and 100,000 units is considered a sufficient therapeutic dosage even in fulminating cases, if given intravenously. Owing to the use of proteolytic enzymes in preparing the serum the risk of anaphylaxis when given by the intravenous route, has been diminished. The effect is purely antitoxic and recent experience in the Middle East shows that it is fleeting and temporary.

**Practical results**—The treatment of bacillary dysentery with antidysenteric serum has been practised now for over thirty years.



There appears to be remarkably unanimity of opinion about its general efficacy in combating the toxæmia and in shortening the course of the disease, but the results until recently were by no means so striking or convincing as in other forms of scientific serum therapy—antitetanic or antidiphtheritic for example

In the serum treatment of bacillary dysentery in children the *intrapertoneal method* has been employed H Knauer (1926) after four years experience of the treatment of bacillary dysentery in infants and children considers that the initial dose of serum should be relatively large and finds this route a convenient one By this method a total of 100-300 c c may be given to one

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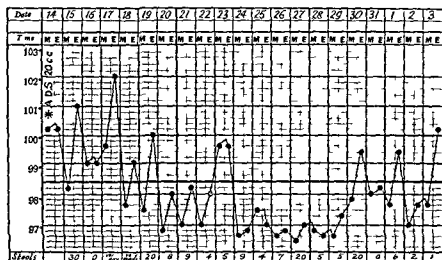


Chart 2—Bacillary dysentery (Shiga) treated by injection of antidyenteric serum

patient by repeated daily doses The injection of the serum in this way is followed by a rapid decrease in the toxæmia H W Joseph and W C Dawson (1921) in America administered antidyenteric serum to twenty children of from six months to four and a half years of age Polyvalent serum in doses of 20-50 c c was injected and in some instances as many as six doses were given at intervals of twenty four to forty eight hours The Rockefeller Shiga antiserum was employed Subsequent reactions were slight and general improvement was noted twenty four hours afterwards

It is necessary that the serum should be given early in the course of the disease In very sick children the intramuscular route is contra indicated on account of the pain elicited at the site of the injection M De Biehler (1922) thinks that serum rash which is common in children can be avoided by giving calcium chloride

**Treatment by sensitized dysentery vaccine**—Boeckneke's *Dysbakteria* (see p 113) or a polyvalent sensitized dysentery vaccine has been employed extensively in Germany, especially in the treatment of children. Schuttenhelm (1918) and Schelenz (1918) reported favourably on this combined

specific treatment in both acute and chronic cases. Gross (1918) considers that in the very acute case, where the body is incapable of reaction the vaccine is of no value. By the combined method of serum and vaccine three subcutaneous injections of the latter are given daily in doses of 0.5, 1.0, and 1.5 c.c., together with a small dose (10-30 c.c.) of antidyenteric serum which may be repeated. This vaccine treatment is harmless, simple and cheap and may be used in mild cases. Dantwiz (1925) after four years' experience of it is in favour of continuing with this method of treatment, especially in children.

Good results have been recorded by R. Korbach and A. Gross (1920) from intravenous injections every fifth day of doses of vaccine gradually increased from five to sixty million. L. Rogers and J. W. D. Megaw (1930) advocated a sensitized Shiga vaccine made by mixing cultures with antidyenteric serum at 37° C for several hours, washing in sterile normal saline and sterilizing at 56° C for one hour. Doses from 50-200 million sensitized bacilli can be used.

**Treatment of pregnant women**—In pregnancy bacillary dysentery should be regarded as a serious event owing to the likelihood of abortion. The use of aperient salines should be carefully regulated for the same reason, and it is advisable to give half doses.

**Treatment by specific bacteriophage.**—F. d'Herelle has claimed that favourable results have been obtained in suitable cases by the administration of bacteriophage, but the results so far are not, to the critical eye, very impressive.

A. Compton (1929) prepared a therapeutic 'phage' by putting up a mixture of four phage strains against sixteen hour broth cultures of two Shiga three Flexner, six Hiss one Sonne and one Gay strain. Complete lysis was obtained in a few hours at 37° C. The lysates after twenty four hours' incubation, were mixed, filtered through infusorial earth and an L<sub>2</sub> Chamberland candle, and distributed in ampoules in quantities of 2 c.c. Each patient takes three ampoules by the mouth daily.

W. Fletcher and K. Kanagarayer (1927) in the Malay States found that the bacteriophage they prepared was stronger for Shiga than for Flexner, and noticed that, though it seemed to have some effect upon a Shiga case it had no influence upon twenty two Flexner cases subsequently treated. F. M. Burnet, M. McKie, and I. J. Wood (1930) report favourably on the treatment of young children attacked by dysentery in whose faeces there was an absence of phage.

J. Taylor, S. D. S. Greval, and U. Thant (1930) subjected the phage treatment to a critical trial with adequate controls. There were twenty controls to twenty six of bacillary dysentery and the phage used was active to a dilution of 1:100. The dose was 2 c.c. given orally three times daily. The results were inconclusive. They considered that no significant difference was observed either in mortality or in shortening the attack.

**Treatment of special symptoms** *Mouth*—The mouth must be kept clean by means of special mouth washes (e.g., Lavaris), and by swabbing the tongue and the gums frequently with glycerine and borax.

*Abdominal pain* is best relieved by the application of hot water bottles, turpentine stupes, or the Japanese hot box, i.e., a tin box containing slowly burning charcoal (known under the name of Istra), three or four of which should be sewn in flannel and placed upon the abdomen.

*Tenesmus and dysuria* are best relieved by hypodermic injections of morphia or by the insertion of cocaine and morphia suppositories. Hot douches into the rectum slowly administered by means of a tube and funnel have also been found to be of value. The rectum can be lavaged with warm saline solution, boracic solution (1 dr (3.8 gm) to 1 pint of water) or 0.5 per cent tannic acid. The temperature of the douches should be about 104° F (40° C).

*Anal irritation and erosion* which are consequent upon the frequent and acid stools are best treated by thorough cleanliness and the application of lanoline, castor oil or vaseline to the parts. Naturally it is very important that bed sores should be guarded against.

*Collapse*—Should signs of a collapse be imminent as indicated by a sudden fall in the pressure the patient must be kept warm with hot water bottles and stimulated with brandy by the mouth or by enema and blood transfusion should be given.

*Vomiting and hiccough* should always be regarded as serious symptoms. Hot stupes should be applied to the abdomen and the patient given ice to suck, or small quantities of champagne. Arrowroot and brandy 2 drachms by the mouth often exert a sedative effect. German workers have advocated amidopyrine in large doses and also cocaine.

*For flatulence and meteorism* charcoal biscuits, granular charcoal or charkaolin are useful.

*Toxæmia*—R. Gantenberg and others in Poland (1939) have found blood transfusions of very great value especially in dehydrated cases. They used citrated in preference to defibrinated blood. For severe cases four blood transfusions have been given weekly together with daily intravenous salines. Under war conditions plasma or dried reconstituted plasma appear to be equally efficacious.

H. Otto (1940) found that subcutaneous injections of adrenalin were beneficial.

#### CHRONIC BACILLARY DYSENTERY

The specific organisms which caused the initial trouble, the dysentery bacilli, play little part in the terminal stages of this disease so that the destruction of the mucous membrane and its replacement by granular tissue has to be regarded as the aftermath of their activities. The problem is a mechanical one; the efforts of the practitioner should be directed towards diverting the faecal stream as much as possible from the large intestine and putting it in a state of almost complete rest so that healing may have a chance to take place.

The line of treatment here advocated may be divided into three headings: dietetic measures, intestinal medication and operative interference.

*Dietetic measures*—The diet should be carefully regulated, monotony being avoided. The author considers it a mistake to starve the patient; he should be provided with as much simple and easily assimilable food as it is possible for him to tolerate. The main object

should be to stimulate the recuperative powers of the body so as to aid in regeneration of the intestinal mucous membrane. Oils and fats are particularly useful, because they tend to lubricate the raw surface of the bowel—thus helping to promote healing—and also, possibly, because of their vitamin content. In principle this is the policy advocated by J. P. Lockhart-Mummery and others in the treatment of ulcerative colitis and other chronic diseases of the colon.

If the patient has a desire for food, he should be permitted eggs, fish, milk puddings, jellies and plenty of butter and bananas. Apparently it is not the nature of the faecal residue which irritates the large bowel, but the fact that matter of any kind is passing through.

In the milder stages of this condition, that is, when characterized by diarrhoea without any grave constitutional disturbances, treatment by medicated enemata sometimes appears to be followed by good results, and it should be tried as a preliminary measure.

**Intestinal medication**—The bowels should be cleared out by a small dose of castor oil followed by a large enema of hot water (2–3 pints (1,700 c.c.) to which 2 drachms (7 gm.) of sodium bicarbonate have been added. This enema is intended to remove the mucus and debris which has accumulated on the surface of the bowel and as such it appears to be useful.

The other medicated fluids that are injected are intended to exert some healing action upon the bowel surface. The most efficient of these with which the author is acquainted is *Eusol* but unless this is given highly diluted at first it is apt to be too irritating and cannot be tolerated. The author commences treatment by the injection of a half pint of a dilution of 1 part of *eusol* (Budge's *eusol* is preferred) to 9 parts of water. The enema should be retained by the patient as long as possible usually from five minutes to three quarters of an hour. If this is satisfactory, the subsequent daily injections should be in increasing strength of *eusol*, for instance, on the second day 2 parts of *eusol* to 8 parts of water and so on until half and half solution is obtained. This produces some pain in the lower bowel due to its stimulating action.

**Technique**—The solution should be run slowly into the rectum by a rubber catheter, the patient recumbent on his left side. The catheter should be made of stout rubber and provided with a round terminal opening. Attempts to pass it higher up into the rectum usually tend to create a kink.

When the patient senses that the solution has entered the sigmoid the knee-elbow position should be adopted for five minutes and then he should lie on his right side.

This treatment may be persisted in for 3–4 weeks but if too exhausting injections should be given on alternate days.

H. J. Smyly (1930) reports good results from intestinal lavage with Dakin's (weaker) hypochlorite solution (Solution Dakin's H.C.H.) 4–20 per cent.

solution can easily be tolerated and the strength is increased each day as rapidly as the patient can bear it. Some cases are cured with solutions not above 50 per cent strength, in others, especially those with rectal ulceration, full strength may be necessary. Experience indicates that it is essential for the solution to reach the highest point in the bowel at which the disease is active, and for this purpose 250-500 c c ( $\frac{1}{2}$ -1 pint) generally suffices.

This treatment has been given three times in one day and can be persisted with continuously from two weeks to several months, till rectal ulcers are healed and signs of acute inflammation have subsided.

For rectal irrigation through a colostomy the following apparatus is required —

A cylindrical glass funnel,  $1\frac{1}{2}$  in in diameter, and graduated to hold 10 oz of fluid. The lower part should be provided with a constriction so as to accommodate the rubber tubing and to afford it a firm grip. The tubing should be bound round with a tape ligature.

A rubber tube,  $\frac{1}{2}$  in in diameter, of a length of 2 ft.

A rectal tube, which should be a stout catheter of at least  $\frac{3}{8}$  in in diameter, with a big round terminal opening.

A bulbous glass connecting tube for joining to the rectal tube.

A narrow tube necessary for securing all junctions tightly.

Rubber gloves for the operator's hands, and a plentiful supply of vaseline.

#### MEDICAMENTS FOR COLONIC IRRIGATION\*

**Silver salts.**—*Albargin* (silver gelatose) 20 gr to 20 oz (1 pint) of normal saline, a 0.25 per cent solution. *Argyrol* (a vegetable protein compound of silver) 40 gr to 20 oz (1 pint) of normal saline, a 0.5 per cent solution. *Argyrol* contains 30 per cent silver and can be given in a strength up to 1 per cent (80 gr to the pint).

*Silver nitrate* (10-20 gr to 1 pint distilled water) should be applied only when acute symptoms have disappeared. An enema of 3-4 pints of warm water containing two or three teaspoonfuls of sodium bicarbonate can be used and when the bowel is empty 2-3 pints of silver nitrate solution injected slowly every three days. The solution must be at 110° F and can be retained for half an hour to one hour.

Note that all silver compounds are soluble only in cold water.

H. J. Smyly recommends the use of these silver salts, even silver nitrate, in stronger solutions than those usually recommended. They all have the disadvantages of being expensive and likely to cause argyria. The latter can be obviated by making it a rule that, if the solution is retained, it should be followed by a large injection (2-3 pints) of hypertonic salt solution to precipitate the silver.

H. Lippelt (1938) introduced *Targasin*, a colloidal combination of albumin with diacetyl tannic acid silver salt. It has no appreciable action upon the mucosa and is well tolerated by the mouth in two tablets three times daily. It exerts an inhibitory effect upon the dysentery bacilli and can be given by enema.

**Bile extract** (*Fel bovinum purificatum*, 20 gr to 2 oz of water) added to the enema is said to increase the peristaltic action of the colon and so to reduce flatulence.

**Bismuth subgallate** (*dermatol*) can also be given by the mouth in doses of 30-90 gr daily. As a retention enema in a 5 per cent solution.

\* See also Chapter XXIV

suspended in 8 oz of olive oil, for ten days consecutively, it has a soothing and healing effect in ulcerated cases. Can be used in a strength as high as 10 per cent.

**Bolus alba** (kaolin, 3 drachms to water, 1 oz., used in suspension) can be given as a retention enema.

**Etherol** (olive oil, 12 fl oz and ether, 6 drachms, well mixed) can be used as a retention enema (J. G. Willmore). This should be injected as the patient is going to sleep. The foot of the bed should be well raised, and a pad and T bandage applied to the anus, the solution should be retained all night.

**Glucose** may be given as an enema in the strength of glucose 1 oz. to 1 pint of normal saline.

**Ichthyol** (ammonium ichthosulphonate) in 0.5-1.0 per cent solution. The ichthyol should first be dissolved in a few drops of glycerin, and the requisite amount of water added. Two pints of this solution should be injected slowly into the bowel and retained as long as possible.

**Kamillosan**, a preparation of chamomile flowers (*Matricaria chamomilla*) is employed in a strength of 2 drachms to 1 pint of warm water. It has an anodyne and antispasmodic effect (Spicer and Co., Watford Herts).

**Linseed**—An infusion of *Linum usitatissimum* has a soothing effect on the bowel. Three handfuls of whole linseed are added to eight pints of water. The whole is brought to the boil quickly and allowed to simmer for two hours, it is then strained and diluted. It is advisable to use it as thick as possible. Give on alternate days. An enema of 2 per cent sodium bicarbonate (1 pint) is advisable two hours beforehand.

**Mercurochrome** should be given dissolved in normal saline in a 1 per cent solution (4 gr. to 1 oz.). A few drops of dilute acetic acid may be added. It is used as an intestinal disinfectant in a 1 to 2 pint enema.

**Milton**, a disinfectant and deodorizer (sodium hypochlorite, sodium chloride and small quantities of chlorate, sulphate and carbonate and calcium chloride) as an enema in strength of 1 fl. drachm to 2 pints of warm water.

**Potassium permanganate** as an oxidizing agent for destroying intestinal bacteria and their products in a strength of 1 gr. to 1½ pints, may be given with safety twice daily.

**Slippery elm** (*Ulmus fulva*) is used as a demulcent. Two sheets of the bark 12 in. by 8 in. are cut into fine shreds and immersed in 8 pints of water. The liquid is then brought slowly to the boil and allowed to simmer for two hours and strained.

**Saccharated alkaline saline solution** (J. G. Willmore) is prepared as follows—

Kitchen salt (NaCl)	1 large tablespoonful
Sod bicarb	1 " "
White sugar	2 " "
Warm water	2 quarts

Two pints can be tolerated.

**Tannic acid** (40-60 gr. to 1 pint of warm water) is most useful on account of its astringent effect, in cases where there is much bleeding. In cases of hæmorrhage, hypertonic saline solution (NaCl 120 gr. to 1 pint) with the

addition of eusol is soothing and effective and may be followed by injection of tannic acid

Solutions of tannic acid for the healing of ulceration may be made up as follows —

Tannin	5 grm
Tinct opu	1 c c
Arrowroot	15 grm
Water to	1 litre

Half a litre to be injected slowly

**Solution for tenesmus and sphincteric cramp.**—A starch and opium enema is very useful on occasions but in case of failure the following is recommended (W. K. Russell, 1932) —

Calc chlorid	10 grm (154 gr)
Mag chlorid	5 grm (77 gr)
Sod bicarb	5 grm (77 gr)
Omnopon	0.04 grm ( $\frac{1}{2}$ gr)
Tinct bellad	3.0 c c (51 mins)
Water to	20 litres (4½ gallons)

A pint or more to be used at a time

**Ispaghul.**—For centuries it has been the custom in India to treat cases of chronic diarrhoea and dysentery empirically with the seeds of Ispaghul (*Plantago ovata*)

Undoubtedly when eaten in their natural state these boat shaped seeds are beneficial. They may be chewed when a gelatinous substance exudes, which acts as a demulcent, or the pulp, made into a paste as "Chulka", which is sold in the bazaars of Bombay, may be taken in doses of one teaspoonful, three times daily, and exerts a soothing effect.

A glucoside *aucubin* is present (R. N. Chopra 1930), but it is physiologically inactive. The action of ispaghul is mechanical, being due to the mucilage in the superficial layers of the seed which is not acted upon by the digestive enzymes, and passes unchanged through the small intestine. It coats the inflamed and ulcerated mucosa and protects it from irritation thus enabling it to heal. When the seeds are taken in large quantities they swell up with water, increasing the bulk of the intestinal contents, and thus relieving constipation.

**Abdominal massage**, with the idea of promoting the nutrition of the bowel, should be employed, unless it causes increase of pain and peristalsis.

**Sulphaguanidine**—The reports on this sulphonamide so far received seem to indicate that it is of distinct value in chronic bacillary dysentery (see p 94)

**Nipectin**—American workers have discovered in pectine and pectinates, the metal derivatives of pectin a specific substance for the treatment of bacillary dysenteries and allied conditions. Pectin is the intracellular cement of the cell wall tissues in fruit and succulent vegetables, especially in citrus fruits possibly its presence in apples explains the value of Moro's apple dietary. The commercial product is

obtained from the rind of citrus fruits and from apple "pomace" (in the manufacture of cider). When mixed with acid, sugar and water, it forms a jelly and with metals assumes a colloidal form. Silver and nickel pectinates appears to possess definite bactericidal properties and the latter, moreover, functions as a catalyst and assists in the absorption of vitamins.

Nickel pectin compound is dispensed by Eli Lilly & Co. as "Nipectin", when mixed with an equal volume of icewater it has a faintly acid taste and, in order to prevent the formation of gummy masses, it should be sifted into food with constant stirring. The dose is large in children and adults it ranges from one to four tablespoonfuls given three times a day, and even as frequently as every three hours, till the stools become faecal.

The value of this preparation in the treatment of chronic bacillary dysentery, as well as in intractable ulcerative colitis, has been emphasized by T. T. Mackie, L. H. Block, A. Tarnowski and B. H. Green (1939) have given it an extensive trial in 95 cases of chronic bacillary dysentery, and a definite improvement was observed in every one, both in appearance and general condition. They consider that it possesses definite anti-haemorrhagic properties.

**Surgical treatment**—The author has no hesitation in advising early surgical interference whenever medical measures fail. The indications for operation should be based upon signs of toxic absorption, intestinal haemorrhage, and sigmoidoscopic appearances of the bowel indicating grave destruction of the mucous membrane. It is not justifiable to postpone operation until the patient is almost in extremis. Should he continue to lose weight with medicated enemata it is an indication that such measures are not meeting with continued success.

Three methods which are represented by several operations, may be considered: (1) through and through lavage by appendicostomy, (2) valvular caecostomy, and (3) ileostomy. The object of all is to promote faecal drainage.

Colostomy, except in the rare event of stenosis, can have no place in the treatment of dysentery, for, should the disease be grave enough to warrant operation, the whole of the large intestine, and certainly the caecum, will be in an ulcerated condition, so that there can be no reason for leaving diseased bowel, such as the caecum proximal to the opening.

**Appendicostomy and valvular caecostomy** (see p. 458)—These operations may be considered together, as in the main their actions are identical, and may be illustrated by the following—

An ex-soldier of thirty was operated upon in 1924 after suffering continuously for three years with chronic bacillary dysentery to which he nearly succumbed.

He contracted bacillary dysentery of a mild degree on the Somme in 1916 and had spasmodic recurrences till 1919, when he was demobilized. In 1921 he had recurrences with blood and mucus in the stools every few months and again in 1922 and in 1923. He was treated at first for amoebiasis with emetine



injections, but no improvement took place and he was admitted to hospital in May, 1923, when a diagnosis was made by sigmoidoscopy, by agglutination tests and by examination of the stools. He was in a severe condition with continuous diarrhoea, emaciation, remittent pyrexial attacks and, eventually, parotitis and peri-arthritis. Appendicostomy was tried and proved a failure, as did also bowel lavage with eusol solutions etc.

Valvular cœcostomy was performed in April 1924, and subsequently the bowel was lavaged daily with hypertonic saline. This treatment proved a success and he was discharged wearing a colostomy belt. He is now in good health and physical condition, and has put on over 3 stone. It has been impossible to close the cœcostomy opening on account of the destructive process in the large intestine, and he continues to pass blood and mucus *per rectum* daily.

In valvular cœcostomy œdema and thickening of the cœcal walls may render the introduction of a Paul's tube difficult so that provision should be made before the peritoneal sutures are inserted. Some surgeons prefer not to open the cœcum for several days after its head and the adherent appendix have been sutured to the abdominal wall. Usually



Fig. 15—Tampon tube

after insertion the tube tends to become loose when the liquid and offensive faecal material escapes into the dressings. This discharge is extremely irritating to the skin which should be protected by liberal applications of castor oil and ambrene. A colostomy belt should be fitted as soon as practicable.

Unfortunately complete drainage of faecal material is not obtained even when the cœcum is opened in this manner, for peristaltic movements continue to drive a certain amount of the faeces along the colon. In order to combat this A. L. Gregg (1926) devised a tampon tube (Fig. 15) consisting of a soft rubber bulb which soldered round the rectal tube, can be inflated. With the bulb B deflated the tube A, is passed through the cœcum until the bulb is situated in the ascending colon (Fig. 16). Gentle inflation by means of a syringe through the tube, C, prevents the bulb from being returned through the wound. A glass rod D, is now passed through the tube, A, at skin level as an anchor to prevent displacement of the bulb by peristaltic pressure. The lumen of the ascending colon is thereby blocked, so that the upward passage of faecal material becomes impossible. At the same time the central tube, A, permits colonic lavage, reflux being prevented by

a simple clip T. By this means the benefits of appendicostomy lavage are gained while drainage is assured.

When once an open cæcostomy has been established the patient may be expected to improve, but such an improvement does not unfortunately, do away with the attendant's anxieties for the difficult problem of when to close the wound has to be decided. Patients naturally object to being left with a permanent colostomy.

After some months of disuse a severely ulcerated bowel may become so stenosed that any attempt to close it is doomed to failure on account of obstruction. This condition has been observed in three

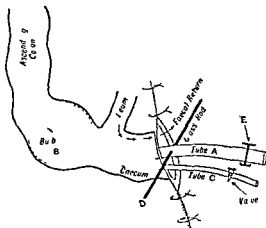


Fig. 16—Diagram showing tampon tube in position

instances and it demonstrates the need for constant attention and supervision. Should evidence of stenosis be observed the patient must be warned that closure of his wound has become impossible. It is on this account that most authorities prefer when closing a cæcostomy wound, to inspect the whole of the large intestine through a mid line incision for then should constriction or stenosis of part of the large intestine be observed it can safely be removed and an anastomosis performed.

The following are indications for closure —

(1) The general clinical condition. The patient should have gained in weight and in general health the temperature should be normal and no evidence of toxic absorption should be present.

(2) The absence of ulceration of the colon. To determine this it is necessary to examine the inside of the colon, this is done by sigmoidoscopy, the proximal by cystoscopy.

(3) The absence of hæmorrhage from the efflux for some considerable period and of pain when the fecal material passes through the colon. This may be ascertained by applying a firm dressing to the cæcostomy

wound after withdrawal of the tampon tube, in order to hinder faecal exit through the wound

**Ileostomy** (*see also* p 460)—Ileostomy in continuity—unless performed after the method of Harvey Stone—may allow passage of faeces into the caecum and, in general, a terminal ileostomy is preferable, especially in long standing cases

Ambrene, a wax preparation, is effective in protecting the skin from irritation

#### TREATMENT OF COMPLICATIONS

**Arthritis**—Dysenteric arthritis with effusion is best treated by placing the limb on a back splint by application of Scott's dressing, by radiant heat treatment for half an hour daily, and later, when absorption has occurred by massage When the joint cavity is greatly distended with fluid aspiration generally relieves the pressure temporarily In addition to the local treatment of the joint detailed attention to the bowel is necessary Therefore lavage with eusol or with sodium bicarbonate should go hand in hand with the local measures B Hughes and H S Banks (1920) recommend early aspiration of the joint and injections of 5 c c of ether into the joint cavity A general anæsthetic is required Under modern conditions sulphaguanidine treatment is indicated

**Eye symptoms**—Conjunctivitis should be treated by local applications of boracic acid and irido cyclitis by instillation of atropine drops (1 grain to 1 oz of water) combined with an eye shade Attention must be devoted to bowel treatment

**Parotitis** may become suppurative, and should therefore be taken seriously It should be treated by fomentations and strict attention to the hygiene of the mouth

**Malaria**—The complication of malaria should never be overlooked, especially when it is a primary infection with the subtertian parasite In this case primary attention must be paid to the malaria aspect An intramuscular injection of quinine bi hydrochloride 12 grains (0.76 gramme) should be given, reinforced by atebrian (0.1 gramme) three times daily for at least ten days (*See also* under Malarial Dysentery, p 268)

**Prognosis.**—The prognosis in bacillary dysentery depends very much upon the intensity of the particular epidemic and on the age and physical condition of the patient It is not possible to lay down definite rules, as the data upon which one can base an estimate are somewhat insecure, but prognosis is by no means good in small children The disease is often fatal, also, to young adults, especially when they hail from countries such as Australia and New Zealand (as during the 1914-18 War), where bacillary dysentery is unknown or very rare

In cases with persistent vomiting or with collapse, the prognosis is not good, while a persistent hiccough may be regarded as being, almost invariably, a fatal sign The outlook is not good, also, in those cases

which, from the start, pass stools containing a large amount of dark altered blood, or greenish coloured sloughs

Patients suffering from valvular disease of the heart do not bear the physical strain of bacillary dysentery well, nor do women in advanced stages of pregnancy. As has been mentioned, primary attacks of subtertian malaria in bacillary dysentery are a dangerous combination, so also is broncho pneumonia, lobar pneumonia, beri beri, scurvy, Bright's disease, tuberculosis, or other grave constitutional disturbance.

C Froemsdorff (1923) quotes figures obtained from reliable German sources extending over the period 1916-20. In 1916, in a series of 12 cases, the death rate was 8.33 per cent, in 1917, in 109 cases, it was 29.35 per cent, in 1918, in 277 cases, 14.07 per cent, in 1919, in 68 cases, 8.82 per cent, and in 1920, in 59 cases, 18.55 per cent. In the whole series of 525 cases, 415 recovered (79.04 per cent), 22 were improved (4.19 per cent), and 86 died (16.33 per cent), and in 2 cases (0.38 per cent) the condition remained unchanged. The death rate was high, especially in elderly patients and in those who were greatly debilitated as the result of war privations. This is by no means an exceptional series, for in the industrial districts of Westphalia the death rate from this cause stood at 10 per cent. Out of a series of 210 cases, whose subsequent career could be traced over a period of six years, in three, or 1.43 per cent, the disease became chronic. The figures from British sources during the 1914-18 War do not convey much information on this subject and have been dealt with by the author in the Official History of the War.

**Natural and acquired immunity**—It is difficult to write about immunity to bacillary dysentery because of the paucity of accurate observations, but the following generalized statements may be made.

There appears to be no *natural immunity* to bacillary dysentery, the prevalence of the disease is unaffected by race and it is as frequently met with in coloured peoples as in those of European descent. Although it is common in every decade of life, there is some evidence to show that man is more susceptible during the first five years of his existence, and in those countries where the disease is prevalent, the mortality among small children is in marked disproportion to that among the adult population. It has been noted that recent arrivals in tropical countries appear to be more susceptible than are residents.

One attack of bacillary dysentery confers a certain amount of *acquired immunity*, but the duration of this is still uncertain. It may be possible to demonstrate the specific agglutinins of the dysentery bacillus for nearly one year after the cessation of the attack. It must be taken into account that immunity may be produced towards one bacillus, while at the same time a greater susceptibility to other dysentery organisms may develop. Ingestion of a sub-infectious dose may convey the immunity to those who have shown no external evidence of the disease.

Attempts have been made actively to immunize man against the

disease by prophylactic vaccination, but so far they have not apparently, been attended by great success. Attempts at passive immunization by injection of antidysenteric serum appear to afford a protection which lasts from four to six weeks.

### PROPHYLAXIS

Personal prophylaxis consists of careful attention to personal hygiene, of care in the conservation and preservation of food in the tropics, and, especially, of taking precautions against contamination of articles on the table or in the kitchen.

Stools which are required for bacteriological purposes should be dispatched to the laboratory in sterile receptacles with well fitting lids. Disinfection of *fæces* is necessary and those passed by dysenteric patients should be protected against the entry of flies and sterilized, as far as possible, by pouring over them crude carbolic or Jeyes' fluid.

Water must be sterilized, it should be boiled before use and efficiently protected against subsequent contamination. Appropriate measures should be taken with ice, fruit and vegetables in localities where bacillary dysentery exists.

Milk also can be infective, and becomes contaminated through the vessel in which it is stored, by addition of infected water, or by *fæces* of infected flies. In tropical and subtropical climates all milk should be pasteurized or boiled before use and then properly protected against flies, dust and other contamination.

The danger from flies has already been discussed and it is hardly necessary to draw further attention to the murder-bearing flight of these insects from latrine to larder. The common breeding grounds of the house fly—the manure heap, the dustbin, and the latrine (especially the dry closet)—demand especial attention.

**Nursing.**—Bacillary dysentery cases are infectious, and to no one are they more so than to the nurses who tend them. They must be tended, therefore, in wards set apart for this purpose and nurses must be warned of the danger they run and should be trained in prevention of this disease.

**Measures against carriers.**—Every effort should be made to protect the healthy population against carriers. The incompletely cured case, that is, the convalescent who is still passing mucus in the stools, is a danger. No one should be permitted to leave hospital and active medical care, unless he is able to take ordinary food without intestinal upset and it is questionable whether the usual three negative bacteriological examinations of *fæces* are all sufficient in this respect. Therefore sigmoidoscopic examination may reveal ulceration of the rectal mucosa and dysentery bacilli may be isolated then. It is suggested too, that the serum of suspected dysentery carriers should be examined for Shiga agglutinins and those with a titre of 1:25 against this organism should be regarded as suspicious. The introduction of sulphaguanidine (*see p. 94*),

which appears particularly effective in the carrier state should greatly simplify this problem in the future. It has been emphasized that this drug acts most effectively when the faeces are fluid so that it may be necessary to combine it with routine aperients.

**Susceptibility**—In considering prophylaxis against bacillary dysentery emphasis is laid upon the toxicity of the individual bacilli and too little importance is attached to the susceptibility of the victim. There is no doubt that there exists a wide divergence in this respect. This aspect of the subject was studied during the 1914-18 War when it was seen that the mortality rate among British troops was infinitely smaller than that among native levies and ill-nourished, depressed and partially exhausted prisoners of war. W. Fletcher and M. Jepps (1924) regard bacillary dysentery in the East as essentially a disease of poverty; they classify the victims as follows: (1) Europeans with a negligible mortality; (2) Eurasians or well-to-do Asiatics, mortality 2.8 per cent; (3) Native labourers and beggars or vagrants, mortality 25 per cent.

Patients who have recovered from bacillary dysentery usually show agglutinins in their serum, although this fact does not justify the assumption that immunity to further infection is present. It has been pointed out by L. Dudgeon that the only true protection to the body is a healthy intestinal mucous membrane.

**Prophylactic vaccination**—The question whether one attack of Shiga dysentery affords absolute protection against future ones is a debatable point. It has been believed that subsequent attacks of Shiga dysentery are really mementoes of the first attack, but it is more probable that if a period of perfect health has continued for some two to three months and the body weight has been restored, then a further attack is to be attributed to a fresh infection and not to relapse. Flexner infection may occur in persons who had previously suffered from Shiga dysentery, whilst the converse may also take place.

In the tropics practically everybody is exposed to bacillary dysentery. The fouling of the banks of streams by faeces and the washing down of this matter by torrential rains are a constant source of infection, so that it is probable that the indigenous native, more particularly in India, is being constantly immunized against the dysentery bacillus. For at least twenty-five years attempts have been made to produce a method of active protection against bacillary dysentery by inoculation. The direct injection of killed cultures of dysentery organisms, particularly Shiga's bacillus, causes severe local and systemic reactions, and therefore attempts by direct inoculation, so successful in typhoid, have had to be abandoned.

Various methods for immunizing this reaction have been employed, such as the use of cultures killed by eosin or of sensitized vaccines, or the injection of the organism mixed with anti-dysenteric serum. H. R. Dean and R. S. Adamson (1916) found 1:1,000 eosin the minimum degree of concentration necessary to render vaccine atoxic. Similar results were obtained by using

hydrogen peroxide in place of eusol. They recommended a vaccine containing 200 million Shiga bacilli per c.c. inactivated at 58-60° C. for one hour. J. Dudgeon (1919) reported that his experience with eusol treated Shiga vaccines was unsatisfactory.

The Japanese first employed a sero vaccine. Graeme Gibson conducted a research on this subject and found that, although the local reactions were mild, no considerable production of antibody took place. It was concluded that the serum had not only neutralized the toxin of Shiga's bacillus, but also destroyed its antigenic properties. Accordingly, Gibson (1917) introduced a method of giving a vaccine of Shiga's bacillus, together with adsorbed anti Shiga serum, whilst a vaccine of Flexner's bacillus could be added. This sero vaccine was issued in twin conjoined phials, one containing the vaccine, the other antiserum. The doses were given in two portions, the first contained 500 million organisms, in addition to 0.1 c.c. of serum. The second contained 1,000 million organisms, together with 0.2 c.c. of serum. The local reaction consequent upon these injections produced a painful induration, but constitutional reactions were mild. Unfortunately, it was impossible to obtain a satisfactory series of statistics, but since those that came to hand were favourable, it was largely used in France during the later stages of the 1914-18 War.

In Macedonia, in 1918, Gibson's sero vaccine was tried with the following results (L. Dudgeon, 1919) —

	<i>Cases of Dysentery</i>
<i>Non inoculated</i> , 2,096	67
<i>Inoculated</i> , 1,147	14

The results show that a considerable measure of protection had been obtained and that this protection remained for at least a year.

A somewhat similar method was applied in Germany and Austria (Boehncke's *Dysbakteria*). Boehncke and Elzeles (1918) reported that 100,000 persons had been inoculated with this substance without any deleterious effect. The protective inoculation should not be delayed till the dysentery is prevalent, and intervals of five to seven days should supervene between the injections.

In 1925, H. M. Perry and C. J. Coppinger found that vaccines of Shiga's bacillus prepared from anaerobic cultures were much less toxic than those prepared from cultures grown in an aerobic manner. They therefore advocated a mixed vaccine prepared from anaerobically grown Shiga bacilli and aerobically grown Flexner bacilli.

*Subcutaneous vaccines* — W. H. Kauntze (1927) reported on the results of inoculation of 12,000 native porters during the East African campaign in 1916 and 1917, with 1 c.c. of polyvalent dysentery vaccine, and of 47,636 natives with 4 c.c. of the same. No improvement in the death rate from bacillary dysentery took place. He thinks that there is some evidence that inoculation of contacts and of all persons liable to infection cuts short spread of this disease.

H. Brokman and F. Przemycki (1925) have shown that, with Shiga toxin as with diphtheria toxin, intradermal injections cause a local reaction by which differences in individuals can be established. The serum of persons who give a negative skin reaction can neutralize the dysentery toxin, the serum of those with positive skin reactions cannot do so.

L. Otten and L. Kirschner (1925) found that a formalized heated suspension

of dysentery bacilli was preferable to anatoxin (formolized heated dysentery toxin) and caused far less marked local reaction. They claim that these formolized suspensions produce immunity.

M. Sardjito (1926) employed a method of immunization by a lysate (bacteriophage) of Shiga Kruse bacilli, treated with formol, 1 c c of the formol treated lysate, after neutralization with caustic soda, being injected subcutaneously. No after effects are said to be noticeable.

W. Troitzki and his colleagues (1910) have shown that ultra violet rays on *B. dysenteriae* remove toxicity. Vaccines made from cultures so treated will protect against living cultures.

R. Priggo (1910) thinks that effective protection can be obtained solely by inoculation of a preparation containing exotoxin and endotoxin, and the immunizing agents used in this work contain both these factors combined with specific antiserum or non specific absorbent, such as alum. Trials in rabbits and mice showed that it is possible to find a dose of suitable composition and of low toxicity which protects animals against subsequent injection of two lethal doses of combined toxins. The efficacy of this method consists in the appearance of antitoxin in the blood.

**Oral vaccines**—For some time past Besredka has been studying what he terms local immunity in infectious disease. From his work and that of others on local immunity produced in the skin of guinea-pigs against anthrax and other infections, he considered that a similar immunity could be produced in the intestinal canal with dysentery vaccine. In 1922 C. Nicolle and E. Conseil vaccinated two Europeans in this manner, by making them swallow killed cultures of dysentery bacilli, and then, after a period of from fifteen to eighteen days, ingesting living cultures. It was claimed that neither of these two developed dysentery as the result of this experiment, while two unvaccinated controls who swallowed the same cultures died of the infection. There have since been some practical trials of this method. In an outbreak of dysentery amongst troops in Versailles in 1923, the incidence amongst 546 soldiers inoculated by the mouth was 7.69 per cent, as against an incidence of 26.86 per cent amongst 1,070 unvaccinated controls. Similar figures were obtained in Russia in the same year, when a thousand people who had been exposed to dysenteric infection were orally vaccinated with a vaccine of dead Shiga Flexner and allied strains. The subsequent incidence of dysentery was 0.3 per cent among the vaccinated and 3.17 per cent among the unvaccinated controls.

In order to secure contact of the swallowed vaccine with the mucosa of the intestinal canal, Besredka advocated previous administration of ox bile. This is said to increase the absorptive power of the mucous membrane for the molecules of the vaccine, thereby increasing immunity.

In Besredka's now well known *bili* vaccine method the technique adopted is to give before breakfast on three successive days a dose of bile followed by a pill containing the desiccated vaccine. Two hours before the first meal of the day, a tablet containing 20 cgm of desiccated bile is administered orally, followed by a dose of 100 milliards of dysentery bacilli killed by heat. No food is allowed for two hours after the dose, and the same treatment is given on two further consecutive days—three days in all.

Since the publication of Besredka's first paper on *bili* vaccine (1922) numerous reports have been published on the method. Most of these suffer from the fallacy almost invariably found in such experiments: the vaccine comes into use when the epidemic is declining from natural reasons and the decline in the epidemic is then attributed to its use. The literature on this



subject is now very profuse, but it is in such a state of confusion that it almost defies analysis. Reference may be made however, to a few of the more important papers.

C Nicolle and E Conseil (1922) have criticized Besredka's results on the above mentioned lines.

In 1925, C Seyfarth tested this method among the Greek refugees in camp at Phaleron, Greece, and claimed that the onset of dysentery was prevented in 340 refugees vaccinated by the mouth. A Gauthier (1924) reported 30 000 antidyenteric vaccinations by mouth to refugees in Greece and Macedonia. It is claimed that no cases of dysentery occurred among those so treated. Liquid polyvalent vaccines containing 35 000 million bacilli per c.c. were given one hour before food.

In 1927, M N Fulton and G P Berry tried oral vaccination against Flexner's bacillus on children under two years of age in the United States. A vaccine containing 400 million each of five different strains—a total of 2,000 million bacilli per c.c.—was given every month in milk on three successive days to 107 children, leaving 399 untreated infants as controls. Unfortunately the frequency of bacillary dysentery in the two groups was subsequently identical.

En Vaz (1929) and E de Araujo and O Torres declared themselves warm supporters of the oral administration of dysentery vaccine, both for prophylactic and curative purposes, and stressed the importance of thus immunizing a backward and insanitary population.

W. Walker and R C Watts (1930) on the other hand, found that oral bi vaccine (prepared by Biotherapie Co. Paris) failed entirely as a prophylactic against bacillary dysentery. J Pergher and J Van Riel have used a preparation known as anavaccine on the employees of companies in the great Central African lakes and found the results favourable. They conclude that the action of the Shiga anavaccine is strictly specific. Revaccination is necessary at six monthly intervals.

G P Alvisatos (1930) has been giving much larger doses than the usual of 0.15 gramme. His doses are 0.2–0.24 gramme of Shiga bacilli killed at 55° C, and formolized at 0.15 per cent. These are given on five or six days, sometimes allowing an interval of five or six days to elapse between the third and fourth doses. These amounts were well borne by adults but should be reduced to half for children under twelve years of age. It is quite obvious that at present it is impossible to give a final decision on the utility of this method. It has at least the merit of being harmless, since no ill effects have been noted as the result of the administration.

*Inoculation with living dysentery vaccines*—G Blanc and J Caminopetros (1927) found that intramuscular injections in doses of 4 000–6 000 million bacilli only, caused a slight infiltration to appear which disappeared again in three or four days. There was no troublesome elevation of temperature. They concluded that there is neither danger nor inconvenience from the use of a living dysentery vaccine.

# The Protozoal Dysenteries

## CHAPTER X

### AMŒBIASIS : EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

**Synonyms.**—The term amœbiasis includes tropical, endemic, or amœbic dysentery, amœbic enteritis, amœbic colitis, and primary or intestinal amœbiasis.

The secondary manifestations of amœbiasis include hepatic amœbiasis (amœbic hepatitis), amœbic abscess of liver (tropical hepatic abscess), lung (pulmonary amœbiasis), brain, spleen and epididymis. Amœbic ulceration of the skin may also be included.

*French* Dysenterie amibienne, *Italian* Dissenteria amebica, *German* Amöbenruhr

*French* Abscès hépatique amibien, *Italian* Ascesso epatico, *German* Tropischer Leberabszess

*French* Abscès cérébral, *Italian* Ascesso cerebrale, *German* Gehirn abszess

**Definition.**—Amœbiasis denotes infection with protozoal organisms known as amœbæ. Though numerous species are known to inhabit man, one only, *Entamœba histolytica*, is strictly pathogenic. Amœbiasis is therefore an infection with *E. histolytica*, affecting one or more organs of the body, but usually causing ulceration of the large intestine. As has been pointed out by C. Dobell, the aim of this parasite is to infect man without causing death or even deterioration of health. Therefore the production of grave symptoms, such as amœbic dysentery or liver abscess, proceeding to a fatal issue, must be regarded as inimical to the parasite as to its host.

**Preliminary.**—Certain considerations must necessarily preface a systematic description of amœbiasis. Difficulty arises from the fact that amœbic dysentery is not, probably, the most common expression of amœbiasis. The normal habitat of *Entamœba histolytica* is the mucous membrane and submucous layers, where it feeds upon the cells, being enabled to rend or dissolve them by means of proteolytic ferments. In this manner the amœbæ live and multiply at the expense of the tissues of their host who is, in ordinary circumstances, quite capable of compensating for the ravages of these organisms without detriment to health. This state of equilibrium is probably the commonest condition met with in amœbiasis in the tropics and gives rise to the "carrier" or "cyst passer" state. Such a condition causes no outward signs of ill health, and can be verified solely by

discovery of encysted forms of amœbæ in the stools. Such a carrier cannot, however, be described as being perfectly normal, because some lesion or abrasion of the intestinal canal must exist, and, under certain circumstances the nature of which is not fully understood, he may develop amœbic dysentery or—it may be—liver abscess.

The genesis of amœbic dysentery appears to be that the amœbæ, under certain conditions, destroy the tissues at a more rapid rate than nature can repair them. All degrees of ulceration of the intestine may therefore result, from a minimal effect producing a transient illness or diarrhœa, to intense ulceration of the bowel, with destruction of the greater part of the mucous membrane and passage of blood and mucus, containing numbers of active amœbæ. This ulcerative colitis is known as *amœbic dysentery*, but blood and mucus may not be present, only liquid fæces—*amœbic diarrhœa*. Some authorities regard infection of the bowel as the initial focus or *primary amœbiasis*, in such a terminology it is rational to term it *intestinal amœbiasis*. Metastatic manifestations of amœbic infection are best known as *secondary amœbiasis*. When amœbic invasion is arrested in the liver, *amœbic hepatitis* is produced, and this process may result in *amœbic abscess* of the liver. These parasites may produce abscesses in other organs—e.g., in the lung or, very rarely, in the brain, spleen and epididymis.

As compared with bacillary infections, amœbic dysentery is a comparatively mild disorder, causing less serious illness and fewer fatalities, and is less infective and not so readily communicable. It would be an error, however, to infer that amœbiasis may not be severe or even fatal, though such accidents are rare.

It thus becomes clear that the majority of persons infected with this parasite are more or less healthy individuals constituting a source of infection to others because they pass in their fæces infective forms of the parasite. Only a small proportion of such individuals suffer either from manifestations of amœbic dysentery or liver abscess. Under such circumstances they are incapable of communicating the disease to others, since the amœbæ, once in the liver or other organ, have, so to speak, lost their way and, as far as the continuation of their species is concerned, are pursuing a blind alley. Infective cysts, however, are produced in the bowel wall and when excreted spread infection.

**Ætiology.**—The parasite which gives rise to amœbiasis is the *Entamœba histolytica* (see Appendix, p. 531, and Plate XXII, p. 539). Infection with this organism is brought about by ingestion of cysts through fæcal contamination. As a general rule they are delicate structures with feeble powers of resistance, and are readily killed. They are able, however, to survive and remain infective for three weeks if kept in water, and in fæces sometimes for the same time, provided that they are not subjected to desiccation. All unprotected wells are liable to contamination especially after heavy rains when fæcal deposits may get washed into them. Tanks such as are found in most tropical countries, constitute a constant source of infection, as

they serve the double purpose of ablution and defæcation. In the tropics, also, rivers are commonly contaminated by natives, and so are ponds and lakes in the vicinity of camping grounds. In large cities with pure water supplies, amœbic infection has become rare, though still abounding in smaller towns and villages.

### EPIDEMIOLOGY

In contrast to bacillary dysenteries, amœbiasis shows a somewhat localized distribution, it is therefore unlikely that amœbic dysentery, liver abscess, or other complications can commonly break out in epidemic form. It can be concluded, generally speaking, that epidemics of dysentery are bacillary in origin while sporadic cases are due to amœbiasis. The so called 'epidemics' of amœbic dysentery which have been reported especially during the 1914-18 War, should be regarded with suspicion as indicating that there was confusion between amœbic and other forms of dysentery.

When many cases of amœbic dysentery occur simultaneously in a locality, it indicates that patients have simultaneously contracted their infection from a common source, and further indicates that there must be, in that area, a larger number of carriers of *E. histolytica* cysts than cases of dysentery. To make this point quite clear, it must once more be emphasized that the sufferer from acute amœbic dysentery is unable to transmit the disease and is therefore non-infective to others. The Chicago epidemic to be described later may constitute an exception (p. 122).

**Transmission by flies.**—J. G. Thomson and D. Thomson (1916) were the first to note that house-flies (*M. domestica*) could transport cysts and pass them unchanged in the dejecta. In the same year P. C. Flu concluded, from a study of the mouth parts of the house fly and bluebottle (*C. erythrocephala*), that cysts of *E. histolytica* could survive in their intestines. In 1917 C. M. Wenyon and F. W. O. Connor were able to ascertain that viable *E. histolytica* cysts could be demonstrated in fly excrement sixteen hours after a feed, and moreover, that cresol 1:40 was most effective as a disinfectant for cysts, preventing their spread by insects. P. A. Buxton (1920), in extensive observations on flies in Iraq, dissected 1,027, and of these 63 per cent contained 'apparent' faeces, and 0.8 per cent cysts of *E. histolytica*.

From this it can be concluded that, under tropical and sub-tropical conditions, house flies may act as disseminators of amœbic dysentery.

**Transmission by water.**—H. M. Woodcock (1918), as a result of experience in Egypt during the 1914-18 War, concluded that water constitutes the most important vehicle for infection. This was in agreement with similar views entertained by the author. During that time in Egypt, Sinai, and Palestine, he kept records of the two main forms of dysentery, and it became evident that the number of amœbic cases increased after a forward move into enemy territory where the

water was no longer adequately controlled or sterilized, the inference being that troops were being infected from faecally-contaminated well water

Subsequently the author (1925) treated ten cases of amœbic dysentery among the telegraph staff of St. Vincent (Cape Verde Islands), where amœbic dysentery constituted the chief form of bowel disease amongst Europeans. The sole source of infection common to all lay in water brought from Lisbon which was stored in large tanks liable to contamination. A similar instance has been reported by R. Hegner (1934) in Guatemala.

The epidemic of amœbic dysentery in Chicago during the summer and autumn of 1933 (June 1st to December 31st) was the first recognized water borne outbreak and the best known extensive epidemic of this disease in a civilian population.

During the epidemic period which coincided with a Century of Progress Exhibition, there were approximately 8,500,000 out of town visitors to Chicago, resulting in unusual congestion. Only one focus of infection was discovered, namely, two hotels which were served, in part, with a common water supply. During this period a total of 1,409 cases was brought to light, even with incomplete reporting. Approximately 75 per cent had had contact with one or both of the hotels with the result that amœbic dysentery contracted from this source was reported subsequently from 400 cities in America.

There was a particularly high incidence late in June, during the latter half of August, and early in October. Of those exposed during the peak periods some 5 per cent acquired the disease. Generally speaking, the more prolonged the exposures at these hotels the greater the hazard of infection. The excessively high rate of clinical dysentery was in strong contrast to the results of previous observations on this disease and may be explained by the unusually massive doses of infecting organism.

The incidence of carriers among employees of the two hotels was high (37.8 and 47.4 per cent), and was found to be much higher among those who usually washed on the upper floors which were supplied with contaminated water. Vigorous measures directed to prevention of the spread of infection by carriers among the food handlers were ineffective.

The principal if not the sole means of spread of this epidemic was through water polluted within one of the hotels. The sewers in both hotels were overloaded to an unusual degree during the period of the epidemic, owing to excessive rainfall and unusual pressure on accommodation. The source of pollution of the water supply, which was common to both, was found to be a rotting wooden plug in an overhead sewer which permitted leakage into the drinking water tank below.

**Transmission by human excreta**—There remains another possibility—that cysts are ingested with green vegetables and raw fruit in those areas, so frequent in the Near East and the tropics, where human "night soil" is used for agricultural purposes.

Human excrement is largely used as a fertilizer for vegetables by Chinese and others, and it requires small effort of imagination to realize that this practice involves dangers, especially when garden produce is

eaten raw It cannot therefore be sufficiently emphasized that no raw vegetables or unpeeled fruit should be eaten in the tropics

J Andrews has demonstrated that amœbic cysts can survive faecal contamination of the fingers and remain viable for at least forty five minutes but are difficult to detect under the nails of adequately washed hands

B K Spector and F Buky (1934) have shown by using the eosin test as an indicator that cysts of *E histolytica* perish rapidly in dry faeces at room temperature

It thus appears improbable that amœbiasis can spread in those countries where sanitation is good as in most European countries and where there are no native servants who may constitute a perennial source of infection

It is difficult at present to assert which of the various methods indicated is of the greatest importance in the transference of amœbic infection This can be solved by more extensive work on these lines

Lowered resistance of the patient to infection is undoubtedly also a factor, and this together with defective sanitation is probably chiefly responsible for the high incidence of amœbiasis in tropical and sub tropical countries

**Age incidence**—In a highly endemic area amœbiasis may probably be acquired at any period of life but it is unquestionably an uncommon disease among European children though this runs counter to popular opinion This freedom from infection in the young may be due in part to the care that is usually exercised by their parents in guarding them against sources of infection The author has never seen a case of intestinal amœbiasis in a European child of under five It is essential that amœbic dysentery in children should be diagnosed with great care mainly because emetine if used indiscriminately may cause severe toxic manifestations

TABLE VIII  
AGE INCIDENCE

Age	Amœbic Dysentery (257 cases)	Liver Abscess (169 cases)	Total (426 cases)
Below 10	0.9	0.0	0.6
11-20	12.5	6.1	9.6
21-30	32.8	37.0	33.3
31-40	28.5	39.8	32.6
41-50	17.4	9.7	15.6
51-60	4.8	6.0	5.6
61-70	2.7	0.7	2.1
71-80	0.4	0.7	0.6

## SEX INCIDENCE

Sex	Amœbic Dysentery (257 cases)	Liver Abscess (169 cases)	Total (426 cases)
Male	90.6	97	93.8
Female	9.4	3	6.2

The youngest case the author has treated was a boy aged  $7\frac{1}{2}$  seen in April 1937. He had been in Nyasaland since his ninth month. First attack of amœbic dysentery at one year. Three severe relapses treated by emetine injections and quinoxyl enemata. In England  $2\frac{1}{2}$  years during which three further relapses with blood and mucus. *E. histolytica* cysts in fair numbers. Cachexia, anæmia, tenderness and thickening of colon. E.P.I. (gr. 18) and quinoxyl retention enemata. Fæces examined daily, no more *E. histolytica* cysts seen. Permanently cured.

Amœbiasis in native children is probably by no means uncommon. It is improbable that they can contract it while being breast fed, a period which may be considerable, after that however they have ample opportunities. H. M. Perry and H. J. Bensted (1929) have shown that amœbiasis in infants occurs commonly among the poorest inhabitants in Cairo, especially after weaning. According to their statistics, *E. histolytica* was found in 18.9 per cent of infantile dysenteries. A. G. Biggam (1932) recorded a case of amœbic dysentery in Cairo, in an Egyptian child three months of age who also presented an amœbic abscess of the liver. D. G. Willets (1914) found that amœbic dysentery constituted 25 per cent of all dysenteries in Filipino children. In the author's (1941) series of 535 consecutive cases, the majority occurred between 20-40, a small proportion between the fifth and sixth decades, only eight above that age. There were only eight cases under 20.

In India P. V. Gharpure and J. L. Saldanha (1931) have published a table (Table VIII) based on an analysis of 426 post mortems of amœbic dysentery in Indians. Of these 0.9 per cent occurred below the age of ten, and there were no cases of liver abscess in this group. On the other hand the ten year period of 11-20 accounted for 12.5 per cent of cases and 6.1 per cent of liver abscesses.

Thus it may be concluded that, when acute dysentery occurs in children it is usually of the bacillary form and that liver abscess is extremely rare under ten years of age, probably on account of the lower incidence of amœbiasis in early childhood. C. F. Craig states that the rarity of amœbiasis in children is not due to any inherent insusceptibility to infection but to a lessened chance of contracting it. In family infections which are not infrequent in the southern United States, it has been shown that even the youngest children are affected provided they are not breast fed. The surveys made by E. C. Faust and E. S. Kagy in New Orleans by D. F. Milam



and H. E. Meleney (1931) and by E. L. Bishop and W. S. Leathers show that the height of the incidence curve for *E. histolytica* occurs between 26 and 30 years but that after 35 there is a rapid decline in the incidence.

**Sex incidence**—With equal chances of infection it is probably true that women are as frequently infected as men but European males preponderate in most parts of the tropics consequently a much larger number is infected. Moreover owing to their occupation men are more exposed. The author's statistics in London show that the proportion of males to females was four to one the latter are less susceptible to liver abscess the author having encountered only six cases which suggests that this infrequency may be more than accidental.

**Race incidence**—All races appear to be liable to infection by *E. histolytica* though it is undoubtedly true that Europeans in the tropics as a rule suffer from amoebic dysentery more frequently and severely than do native races. In the Philippine Islands Craig observed comparatively few cases of amoebic dysentery amongst the Filipinos at a time when the disease prevailed among Americans and other white races. A very high percentage of natives is infected as is shown in the statistics of F. J. Walker and others in the Philippines and of Wenyon and O'Connor in Egypt. Comparative freedom from severe symptoms is largely due to partial immunity acquired by constant re-infection since childhood.

**Seasonal incidence**—Amoebiasis in general does not exhibit that seasonal incidence which is so characteristic of bacillary dysentery. Cases may occur at all times of the year though it is doubtless true that certain climatic factors favour the spread of infection and therefore the incidence of the disease. Thus Wagner (1935) in observations extending over eight years found susceptibility of laboratory animals to infection generally higher during the summer than during the winter season. This might explain the greater number of infections commonly encountered in hot climates. In very hot weather profusion of flies may increase the risk of infection by faecal contamination and the rainy season by affording greater chances of dispersion of *E. histolytica* cysts in water may be responsible for many infections.

**Cyst-carriers**—The cyst carrier, cyst passer or cyst excretor state is a condition presenting many difficulties but undoubtedly it plays an important part in the dissemination of the disease and therefore takes a prominent place in epidemiology.

The healthy carrier of *E. histolytica* may be defined as one who has not suffered from dysenteric symptoms and who appears in every respect normal. It is postulated from what is known about the natural history of *E. histolytica* that such a person has living entamoebæ in his tissues. The convalescent carrier on the other hand is one who

has recovered from an attack of amoebic dysentery and still continues to pass cysts of *E. histolytica* without presenting obvious signs of the disease

It is now generally understood that for one individual who is suffering from amoebic dysentery and is passing in his stools active vegetative forms (which are non-infective) there are many who continue to pass cysts and constitute a perennial source of infection. The lesions of the mucosa in these individuals may be minute, so as to be visible only in microscopic sections of the bowel. Thus, in a post mortem on a case of pernicious anaemia in Vienna, J. Hammerschmidt (1919) was able to demonstrate, in serial sections of intestine, invasion of the otherwise undamaged mucosa by amoebae, although neither the clinical history nor the gross pathological picture suggested amoebiasis nor could any lesion be detected by the naked eye.

There are certain considerations in the genesis of the carrier state which must be borne in mind. C. Dobell (1919) and many others have observed that no hard and fast line can be drawn between the typically healthy carrier and the patient suffering from acute amoebic dysentery. These may be regarded as extreme manifestations of one common condition and interconnected by intermediate states which may be seen in different individuals, or in the same at different times.

K. M. Lynch (1934) has expressed the opinion that it is still unsettled whether on occasions *E. histolytica* may not exist in the lumen of the bowel as a commensal. E. Reichenow has expressed the same views and H. E. Meloney (1934) has shown that *E. histolytica* may frequently be found in the intestines in the absence of any macroscopic lesions in the bowel. On the other hand, since the time of N. Macleod (1895) it has been realized that considerable ulceration of the bowel may exist in the complete absence of dysenteric symptoms. Death may even supervene without suspicion of the disease, as in cases noted by the author in the last war, reported by J. M. Cowan and H. Miller (1918) and later by C. C. Lund and J. R. Ingham (1938), who have recorded four such cases.

G. T. Craig has defined the carrier as an individual in whom *E. histolytica* is living as a commensal. In every carrier, cytolysis and superficial necrosis of the intestinal epithelium continually occur in microscopic areas of the intestine. In the majority of cases this is followed by rapid regeneration of the epithelium but in some cases definite ulceration occurs.

C. A. Hoare (1925) was able to demonstrate a similar state of affairs in kittens artificially infected with *E. histolytica*. When killed forty-one days afterwards the intestine appeared to the unaided eye to be normal.

Freedom from infection is apparently not dependent on social status. Thus C. F. Craig (1932) found the carrier rate in 184 physicians from all parts of the United States to be 12.7 per cent. Weinrich and his colleagues found 4.1 per cent in 1,060 American University students,

J J Sapero and C M Johnson 9.5 per cent in naval personnel in the Panama zone. The rate is usually higher in hospital patients. Thus A H Sandford (1916) found 22.5 per cent in 5,000 patients of the Mayo Clinic, S M Tao (1931) 10.49 per cent in 9,588 hospital patients in Peking, W L Christie (1914) 8.4 per cent in similar cases in Borneo, E C Faust (1931) 27.2 in male and 18.1 per cent in female patients in New Orleans. Asylum patients are usually heavily infected, R M Svensson (1928) gives 21.4 per cent in 1,244 lunatics. Food handlers have received special attention: thus A A Philpitschenko (1930) found infection rate of 27.7 per cent in 400 workers in Leningrad. H W Y Taylor (1939) reported that six students in the Medical College in Mukden were attacked simultaneously with amoebic dysentery and the cook was found to be a carrier.

The incidence of cyst passers may be taken as an index of the prevalence of amoebic dysentery in a community. Naturally the number of positives rises in proportion to the number of microscopic examinations made. Thus W C Boeck and C W Stiles (1928) with an average of 1.6 examinations per person found 4.1 per cent in 8,029 persons, but in 505 on whom six examinations were carried out this percentage rose to 15 per cent.

The accompanying table has been compiled from various sources and every effort has been made to make it as complete as possible. It will be observed that wide variation occurs in the incidence of *E. histolytica* infection in various countries.

TABLE IX

	Total number of cases examined	Percentage of stools showing <i>E. coli</i>	Percentage of stools showing <i>E. histolytica</i>
<b>England</b>			
(1) Troops invalided from Gallipoli 1915	971	30.4	23.7
(2) Civilians (Dobell)	3,146	36.0	7.1
(3) Royal Infirmary, Liverpool	450	6.7	1.5
(4) Recruits in camps	1,098	18.2	5.6
(5) Children under twelve (never out of England)	548	11.1	1.8
(6) Asylum cases (Smith and Malins 1918)	207	45.9	9.7
(7) Convalescent dysenteries (Matthews and Smith 1919)	2,355	29.3	13.0
<b>China</b>			
(1) Chinese and foreign in Peking (Faust 1929)	13,617	24.2	20.3
(2) Chinese only in Peking	368	30.9	29.5
(3) Foreigners, all ages (Kessel and Svensson, 1924)	816	17.6	14.1

TABLE IX.—continued

	Total number of cases examined	Percentage of stools showing <i>E. coli</i>	Percentage of stools showing <i>E. histolytica</i>
<b>Java.</b>			
(1) Natives (Brug)	150	—	23.6
(2) Europeans (Brug)	100	—	27.8
<b>Malaya.</b>			
(1) Malays and Chinese (Jepps, 1923)	1,034	14.5	7.7
<b>India.*</b>			
<b>Egypt.</b>			
(1) Hadra prisoners (healthy) (Wenyon and O Connor, 1917)	524	48.6	13.7
(2) Native cooks (Wenyon and O Connor)	87	20.7	11.5
<b>C. and S. America.</b>			
<b>Brazil.</b> Amazon school children (Young, 1922)	249	36.9	22.5
<b>Colombia.</b> Santa Maria (Kofoid, 1926)	—	41.1	53.7
<b>Panama</b> (Faust, 1930)	—	26.8	19.2
Porto Rico (Faust, 1934)	—		
<b>United States.</b>	—	34.2	14.5
(1) Miscellaneous cases (Boeck and Stiles, 1923)	8,029	24.5	6.8
(2) Richmond overseas troops	2,300	43.6	29.1
(3) Home service troops	576	33.9	9.7
(4) Minnesota (Riley, 1929)	500	16.1	1.9
(5) Wise County (Faust, 1930)	460	55.5	45.4
(6) New Orleans (Faust, 1930)	172	34.0	27.9
(7) Pennsylvania (Freshman, 1933; Warwick <i>et al.</i> )	—	13.9	4.1

\* There are no reliable statistics for the carrier rate in India—those which are found in the literature refer to Indian troops serving in Mesopotamia. W. Mac Adam (1918) gives the following figures—

*Previous history of dysentery or diarrhoea*

Cases, 218. Carriers 41 = 18.8 per cent. *E. histolytica*

*No previous history*

Cases 133. Carriers 7 = 5.2 per cent.

*Convalescents. No previous history*

Cases, 154. Carriers 19 = 12.3 per cent.

*Remote history of dysentery*

Cases 216. Carriers 40 = 18.9 per cent. *E. histolytica*

*Recently discharged after dysentery*

Cases 190. Carriers 38 = 19.1 per cent.

J. Dunbar and E. D. Stephens (1930) give the carrier rate amongst Indians in Valparaíso as 21.9 per cent.

It has been pointed out by several of the above mentioned observers, who have made a systematic review of this subject, especially by R. Svensson (1924), that the incidence of intestinal infection with *Entamoeba coli* may afford some indication of the probable rate of infection with *E. histolytica*, indeed, from a consideration of results of research which appear from time to time, it seems that *histolytica* infection may be proportionate to the degree of infection with other intestinal protozoa.

On the whole, in making these surveys, less satisfactory results are obtained from examination of formed than of loose motions.

#### GEOGRAPHICAL DISTRIBUTION OF AMŒBIASIS

Until comparatively recent years it had been supposed that amœbic dysentery was a disease confined to the tropics and a limited area of the subtropics, but since more exact observations have been made, and since it has been the practice to examine systematically large numbers of stools for evidence of protozoa, the range of amœbic dysentery has been greatly expanded. The geographical distribution of the disease—amœbiasis—naturally coincides with that of the causal organism, *E. histolytica*, and as far as reliable records go, this parasite seems to exist wherever there are human beings. In spite of this amœbiasis is more prevalent in tropical and subtropical countries than in the temperate and colder regions of the world. There are reasons for believing that this localization of the disease may depend more upon defective sanitation than upon temperature and climate, but where insanitary conditions co exist with a tropical climate it is found in its most intense form.

Although the relatively greater frequency of amœbic dysentery in tropical populations follows naturally upon the greater incidence of infection with *E. histolytica*, this does not explain the whole story, for it is well recognized that certain complications of amœbic dysentery, especially liver abscess, are more common among Europeans in the tropics than among indigenous natives. It must also be remembered that our knowledge of amœbic dysentery is based, to a great extent, upon a study of the disease as it occurs among Europeans, and that we still possess only a sketchy and inadequate knowledge of the incidence of amœbic cyst carriers amongst indigenous populations.

Although it has been ascertained that carriers of amœbic cysts occur even in Northern countries, amœbic dysentery and liver abscess are extremely rare diseases in these regions, though sporadic cases have been reported in Great Britain, France, Germany and Austria. Soon after the 1914-18 War, the author treated cases of indigenous amœbic dysentery among British troops who contracted the infection in France and Germany. This exceptional occurrence was due, possibly, to the proximity of Indian troops, who were heavily infected.

Amœbiasis becomes more common as the regions of southern Europe are reached and it is now known to be comparatively frequent in South Spain, Italy, the Balkans, Greece, Rumania, and South Russia. In

Asia Minor, Palestine, and particularly in North Africa from Egypt to Morocco, amœbic dysentery and liver abscess are endemic, while throughout the whole of tropical Africa, especially on the West Coast on the Congo, and in British East Africa, this disease is relatively common, the author has seen indigenous cases as far south as Cape Province.

In Asia, there is abundant evidence that amœbiasis is prevalent in Arabia, India, Malaya, Indo China, central and southern China, but the author has not seen cases from farther north than Peiping. On the China coast, especially in Shanghai, the disease is well known. In India the provinces of Bengal and Bombay are heavily infected.

Turning to the New World, amœbic dysentery is rife in tropical America, and it appears to be relatively frequent in the southern United States, especially Texas and South Carolina. In Mexico, Panama and the northern half of South America—Venezuela, the Guianas, and Brazil—it appears to be as frequent as in Asia, and extends as far south as Paraguay and northern Argentina, though from farther south there appears to be no record of the disease. In northern America amœbic dysentery and liver abscess are by no means rare. The State of New York is understood to mark the northernmost limit of the disease, but the incidence of amœbiasis is becoming increasingly recognized. Thus E. S. Kagy (1938) has indicated as a result of studies by the U.S. Medical Corps, that amœbiasis presents a very real health problem and that between 5 and 10 per cent. of the population harbour *E. histolytica*, food handling is held to constitute an important means of transmission.

Amœbic dysentery is well established in most islands occurring throughout the West Indies, especially on the island of Martinique, and it is well known in Malta, Madagascar, Mauritius and St. Helena. Farther east, we find it in Ceylon, Andamans, the Malay Archipelago, Sumatra, Java, and East Indies. Apparently, too, it is found in southern Japan, and is well known in Formosa and the Philippines. In the Pacific Islands we have records of amœbic dysentery and liver abscess in New Caledonia, Fiji Islands, and Samoa, but the Cook Islands and New Zealand appear to be exempt. It is probable that more extended enquiries will show an even more widespread endemicity.

**England**—From a perusal of the extensive literature on this subject little doubt can remain that from time to time genuine autochthonous cases of amœbic dysentery and liver abscess actually do occur in the British Isles.

In the older records are two cases cited by Dickinson. The first was in 1862, a woman of thirty-seven in St. George's Hospital, London, who had ulceration of the colon and in whom an abscess of the right lobe of the liver was found, which, *post mortem*, yielded one gallon of pus. In 1881, a second case, a man of thirty-six, who suffered from severe dysentery followed by liver abscess, was also recorded in St. George's Hospital. In discussing these cases Dickinson made an original

prophecy in regarding ulceration of the colon and liver abscess as cause and effect

R Saundby and J Miller (1909) recorded a case of amœbic dysentery with abscess of the liver in an inhabitant of Birmingham. Amœbæ were said to have been identified in the abscess which was situated in the posterior portion of the right lobe of the liver and measured 5 in in diameter

In 1912, D G Marshall recorded a case of indigenous amœbic dysentery in a ploughman aged twenty six, living near Dunbar, Scotland. He suffered from chronic diarrhœa and was successfully treated with ipecacuanha. Amœbæ were said to have been found in the stools

C M Wenyon (1916) recorded a genuine case of amœbic dysentery in the London Hospital. This was a labourer who had never been out of England and who apparently had contracted the infection while working on a transport lying in the London Docks. A liver abscess was subsequently opened and drained and in scrapings of the wall active *E histolytica* were found. At the post mortem a second liver abscess was disclosed, and there were amœbic ulcers in the large bowel. In the same year two further cases were recorded by G C Low and C Dobell

A S Simpson (1926) recorded what appears to have been a genuine case of amœbic dysentery with liver abscess contracted in England. The case, being correctly diagnosed, was operated upon, a large liver abscess was evacuated and recovery ensued after EBI treatment. In 1928, J C Gilroy recorded a case of liver abscess with amœbic dysentery in an attendant of the Burnley (Lancs) public abattoir. Open operation was performed, but the patient subsequently died

The author, with C B V Tait (1929), recorded yet another case of indigenous amœbic infection. This man a stevedore aged sixty was seen at the Albert Dock Hospital in 1928. He had never left this country, but for forty years had worked on ships from Calcutta and Bombay, and it was from this source that he had probably contracted the infection. Numerous and active *E histolytica* were found in the blood and mucus stools. He had then been ill for over two years with very evident signs of dysentery and had been treated as a case of lead poisoning. Response to anti amœbic treatment in his case was instantaneous

France—M Gaillard and M Brumpt (1912) recorded a case of amœbic dysentery of three and a half months duration in a man of twenty eight who had never left France, amœbæ were found in the stools. J Paviot and C Garn (1913) in Lyons recorded a fatal case in a man who had never been out of France and who had not served in the Army. Free and encysted amœbæ were found in the stools, and a kitten injected with material per rectum became infected and died. L Landouzy and Debré (1914) described a fatal case of amœbic dysentery

in a *bargee* on the Seine, and Labbé (1919) eight cases of indigenous amoebic dysentery in Paris

P. M. Rennie (1922) has recorded five of the author's cases of amoebic dysentery in returned soldiers who originally contracted their infection in France. C. Garin and P. Lépine (1924) consider that amoebiasis was introduced into France on a large scale by Colonial troops during the last War. They have collected a series of 208 cases and two indigenous cases of liver abscess in less than four years, all in the vicinity of Lyons.

**Germany**—Jurgens (1908) first recorded indigenous amoebic dysentery in Germany in a boy of sixteen at the Charité Hospital in Berlin. W. Fischer (1920), in Berlin, recorded two genuinely indigenous cases—a young man who had suffered from clinical dysentery in the Army, and a young woman who was passing blood and mucus stools containing *E. histolytica* with ingested red blood cells. The author treated two cases of amoebic dysentery in returned soldiers who contracted the infection as prisoners of war in Germany.

F. W. Bach (1932) examined the faeces of 1,000 subjects for parasitic protozoa in Germany and found *E. histolytica* cysts in 5.7 per cent.

**Norway**—J. B. Øe (1910) has described an indigenous case of *F. histolytica* infection in a woman who had never been out of Norway and the disease was reproduced by intrarectal injection of the cysts into kittens.

**Russia**—The records from Russia are scanty, but it must not be forgotten that the original descriptions of *E. histolytica* and the classical account of its pathology by Losch (1875) came from that country. The patient was a peasant from the Archangel district, twenty-four years of age, who eventually died from the disease after heroic efforts had been made with drugs then available. The patient was first seen in 1873, and a dog was successfully infected by Losch by injection of faeces *per rectum*. In the Kola Peninsula, which lies well within the Arctic Circle, G. V. Epstein (1931) found a carrier rate of 60.6 per cent in 900 persons, but not a single case of amoebic dysentery.

According to recent surveys amoebiasis appears to be widely spread through Soviet Russia. The figures are as follows:

	No of cases	Percentage of <i>E. histolytica</i>
Leningrad	1,401	20.3
Kola Peninsula	900	60.6
Azerbaijan	1,146	32.5
Armenia	—	17.7
Georgia	570	32.3
Turkestan	1,664	25

**Hungary**.—G. Bodrogi and G. Makara (1939) found in one village 22 per cent and in the Government Hygiene Institute 28 per cent.



**Holland**—W. A. Kuenen (1918) quoted seven cases of amoebiasis contracted in Holland, in four of which there were intestinal symptoms, with active *E. histolytica* in the faeces, and re cited the case of Nolen who in 1908 had medical care of a Dutch fisherman from Vlaardingen who was passing blood and mucus stools with amoebæ containing ingested red blood cells.

J. van der Hoeven (1921) treated a case of indigenous liver abscess in a woman aged thirty nine who had never been out of Holland. Amoebæ were demonstrated in the evacuated pus.

E. P. Snijders (1929) discovered a family in Holland of which three members had suffered from amoebic dysentery.

**United States**—That amoebiasis has been prevalent in the United States especially the southern has long been recognized though it is only in recent years that the disease in its various manifestations has attracted the general attention of the medical profession in that country. The reader is advised to turn to the original account of the pathology of this disease by the older writers. W. Osler (1890) in Baltimore was the first to demonstrate amoebæ in the stools of amoebic dysentery in that country and in the same year there appeared an exhaustive study by W. T. Councilman and H. A. LaFleur a description of the pathology so complete that there remains little to be added up to the present day. They conclusively demonstrated amoebæ (*E. histolytica*) in the tissues in amoebic intestinal ulcers and in liver and lung abscesses. The detailed and accurate drawings of individual amoebæ by G. H. F. Nuttall which illustrate the work leave little doubt in the mind of the critical observer that they were indeed *E. histolytica*.

C. W. Stiles (1922) made an exhaustive study of intestinal amoebiasis in the northern United States and in a microscopic examination of 18 048 faecal specimens of 8 029 persons and in 28 institutions found that 99.9 per cent showed protozoa and 4.1 per cent *E. histolytica*. Of 2 584 soldiers who did not go to Europe 3.5 per cent were infected and of 3 536 soldiers who returned thence 2.8 per cent were infected. The practical facts he states are as follows. In temperate climates the intestinal protozoa of man are by no means of so much clinical importance as had been assumed. The average case of infection is usually of such slight importance from a clinical point of view that it can be ignored. In temperate climates *E. histolytica* is not usually a serious parasite and its presence in healthy carriers is common. Probably no person would question the seriousness of amoebic dysentery in the Southern States.

P. W. Brown (1926) has given an account of cases of American origin observed in the Mayo clinic. They comprised 153 cases with dysentery or liver abscess, 258 cases in which the chief complaint was diarrhoea and 122 carrier cases. The best treatment was found to be the generally recognized anti amoebic treatment with dilute hydrochloric acid for achlorhydria. (This appears to be an

occasion where achlorhydria has been noted in amœbiasis—a fact which requires further study.)

Up to 1933 it cannot be said that amœbiasis had presented a serious public health problem in the United States. Recent events in Chicago, however, show that even in non tropical countries this disease may become a grave matter. Up to 1933 the notification of amœbiasis to the Chicago Board of Health averaged one or two cases monthly. On August 15, 1933 two cases were reported in which the patients had eaten a meal at a certain hotel, and subsequently, with great promptitude, 364 food handlers at this hotel were investigated, with the result that 11 carriers of the infection were detected amongst them. Some seven weeks later a second examination revealed on this occasion no less than 60 carriers, while out of 498 persons who were not connected with the catering department, no less than 100 had *E. histolytica* cysts in their faeces. (The epidemic has already been reported on p. 122.)

It appears probable, from the work of W. E. Frye and H. E. Meleney (1933), that strains of *E. histolytica* in the United States may vary greatly in virulence. C. F. Craig (1935) has collected together the statistics which have been amassed. The positive percentages vary within wide limits but the mean infection rate out of a total of 49,336 individuals is 11.6 per cent. The largest number of individuals examined by a single observer in the United States is 8,029 by W. C. Boeck in 1923. This survey covered four distinct classes, i.e. soldiers with foreign service, soldiers with home service only, persons with no military service, and those of undetermined status. In the first category 2.8 per cent were infected, in the second 3.5 per cent, in the third 8.8 per cent, and in the fourth 3 per cent.

**Canada**—J. E. Bates (1925), in reporting a genuine case of amœbic dysentery in which the infection had been acquired in that country, believes this to be the third authentic instance in the Dominion.

**Central and South America**—From the writings of W. M. James and W. E. Deeks (1924) it is known that amœbiasis is widespread in the Panama zone.

In Colombia, W. M. James (1925) found over 50 per cent of hospital patients infected with *E. histolytica*. Among club servants, waiters and cooks an astonishing incidence of 60 per cent was revealed. In out patients with past histories of dysentery more than this number were found. The damage done by chronic amœbic infection there, he thinks, is worse than that inflicted by chronic malaria.

M. R. Castex and D. Greenway (1926) claim that they are the first to report this infection in the Argentine. Of 504 cases of chronic digestive trouble, 24.5 per cent harboured *Entamoeba histolytica*.

**India**.—Amœbiasis appears to be widespread throughout the Peninsula. It is difficult to state with any degree of accuracy the proportion of the population affected as, from the writings of J. A.

Manifold (1926), there appear to be considerable differences of opinion in this respect (*see* p. 27) ; this subject was dealt with under the section devoted to the carrier problem (p. 128).

**China.**—J. F. Kessel and O. Willner (1925), in the Peking Union Medical College, record that out of 1,800 patients admitted, 7 per cent. were found to be suffering from amoebiasis ; 16.7 per cent. of the Chinese so infected and 30 per cent. of the foreigners were suffering from acute or chronic colitis, while 34.4 per cent. of Chinese cases and 9 per cent. of foreigners were symptomless and apparently healthy "carriers."

**Dutch East Indies.**—From the writings of P. C. Flu (1919) and S. L. Brug (1920), it is known that amoebiasis is a common disease in these islands ; the former finding 10.5 per cent., the latter 12.7 per cent. of the inhabitants infected, while F. H. Ter Poorten (1928) records that of European naval ratings returned from service in these waters about 10 per cent. were found infected with *E. histolytica*.

**Australia.**—Amoebiasis is indigenous to the whole continent of Australia. The author treated a severe case of intestinal amoebiasis in a young English settler who undoubtedly contracted the disease in New South Wales. W. H. Nelson and C. H. Shearman (1918) record the case of a butcher who developed amœbic dysentery in Perth, Western Australia, and also refer to a case of amœbic liver abscess in one who never left the country.

The relative incidence of the two main forms of dysentery, as summarized in various official reports, is given in Table X, p. 136.

TABLE X.

COUNTRY	DATE	OBSERVER	PLACE OF EPIDEMIC	NUMBER OF CASES	DEATHS	TYPE OF DYSENTERY	TYPE OF EPIDEMIC (Age, Army, Prison, etc.)
FRANCE	1917	Laygue G., and Haguenade J.	S of Somme	449	—	Shiga, 36 Flex ner 5, Hiss, 20	Army
	1917	Lancelin R., and Rideau, J.	Brest	202	8	Shiga, 27, Flex ner, 102	Prisoners of war
	1918	Stockey G. E.	Bertuchamp Meurthe Moselle	—	—	Flexner Y	Civil population
	1918	Morand Bezancon and Paraf	Nr Paris	200	—	Shiga 43	Military camp
BELGIUM	1930	Kervenaers	Brussels	170	—	Flexner	Army Garrison June to Sept
GERMANY	1915	Matthes M.	—	—	—	Bac dys Y	Army Mild epidemic Relapses frequent, often worse than initial attack
	1917	Mayrhofer, E. and Von Reuss A.	Baden Leedsdorf	221	—	Shiga Kruse	Civil Fatal cases mostly in children and old people
	1917	Laumpe R.	Dresden	—	—	Dys bac found in 15% of cases	All ages
	1918	Atel R. and Löffler	—	—	—	Shiga Kruse	Res latn Landsturm Origin traced to potato salad, out of 1369 persons who ate it, 27.61% attacked

\* Much of this information has been obtained from the Epidemiological Report of the League of Nations 1933

COUNTRY	DATE	OBSERVER	PLACE OF EPIDEMIO	NUMBER OF CASES	DEATHS	TYPE OF DYSENTERY	TYPE OF EPIDEMIO (Age, Army, Prison, etc)
GERMANY	1928	Buchner, S	Münster	160		Bac. dys in half the cases over 6 mths of age, in nearly all over 2 yrs	
AUSTRIA	1920	Bernstein, S. Klug, D., and Rosenblatt, S	Vienna	901	4%	Shiga, Flexner Y, and Strong in 65%	During and after war
RUSSIA	1916	Meyer, F	—	—	—	Third of cases de- veloped fever, 10 cases, Flex- ner Y	Army
	1916 1930	Koch, J Philipschenko, A A	— Leningrad	— 225	— —	Bac dys epidemic Bac dys in 98% of cases	War time Epidemiological Rept of R S F S R (1933) shows bac dys to be prevalent in Euro- pean Russia to extent of 0.434 per thousand of inhabitants
ITALY	1928	Official statistics	—	—	594	55 deaths due to amebiasis, 72 to bac dys	Bac dys predominates throughout country
SPAIN	1929	Garcia, E	—	—	800-900 per ann	Majority bac	Civil population
YUGOSLAVIA	1919-25	—	—	Decline from 17,532 to 1,311 per ann.	—	Bac dys	Civil population

TABLE X (Cont.)

COUNTRY	DATE	OBSERVER	PLACE OF EPIDEMIC	NUMBER OF CASES	DEATHS	TYPE OF DYSENTERY	TYPE OF EPIDEMIC (Age, Army, Prison, etc.)
BULGARIA	—	—	—	500 per ann	—	Bac dys	Civil population
RUMANIA	1932	—	—	7 265	860	Chiefly bac dys	Civil population
GIBRALTAR	1932	Colonial laboratories	—	—	—	—	In the Colonial lab, bac dys alone re- ported amongst Euro- pean population
CYPRUS	1927-31	Colonial laboratories	—	132 837 per ann '31 in 1931	—	Bac and ameb dys about equal Shiga	Civil population
AFRICA — EGYPT	1902-27	Khouri J	—	—	—	Bac dys prevail- ing form, 65% of cases Shiga and Flexner Bac dys	Civil population
SUDAN	1930	—	—	2 207	552	Bac dys	—
	1930	Official statistics	Khartoum Khartoum and Omdur- man	1 222	—	Bac dys and ameb (ameb prevailing 8 1)	—
	1931	Official statistics	—	81	—	Flexner 37 Shiga 23	—
—	—	Ruding D	—	—	—	Para Shiga bac of Schmitz	Outbreak among Brit officials
SOMALILAND	1929-31	Official statistics	Brit territory	259	—	Bac dys predom- inates 3 cases intestinal ameb biasis	—

COUNTRY	DATE	OBSERVER	PLACE OF EPIDEMIC	NUMBER OF CASES	DEATHS	TYPE OF DYSENTERY	TYPE OF EPIDEMIC (Age, Army, Prison, etc.)
E AFRICA	1917	Pine J H H	—	56	—	Shiga and Flexner 2 cases, <i>E histolytica</i>	E African Expeditionary Force
KENYA	1931	Official statistics	—	1,233	34	35.2% bac dys, remainder amœb	Civil population
UGANDA	1931	Official statistics	—	5365	—	65.7% bac dys	—
TANGANYIKA	1929-31	Official statistics	—	3031	—	2.0% bac dys, 76% amœb	Bacillary infection probably more prevalent than indicated
NYASALAND	1931	Official statistics	—	2270 (60 Europeans)	—	Definite nature of infection ascertained in only 319 cases 50% bac dys	Civil population
ZANZIBAR	1930	Official statistics	—	156	9	Bac dys	Prison epidemic Suggested transmission by houseflies
	1931	—	—	151	—	95 cases bac dys, 5 amœb	—
SEYCHELLES	1931	Official statistics	—	73	7	Bac dys, 6 amœb cases	Suggested introduction by carrier from E Africa
MAURITIUS	1921	Balfour, A	—	11073	—	499 deaths attributed to dysentery, 308 to diarrhoea	Civil population

TABLE X (Cont.)

COUNTRY	DATE	OBSERVER	PLACE OF EPIDEMIO	NUMBER OF CASES	DEATHS	TYPE OF DYSENTERY	TYPE OF EPIDEMIO (Age, Army, Prison, etc.)
MAURITIUS	1931	Official statistics	—	—	—	Shiga Flexner Hiss and Russell	Civil population
MADAGASCAR	1932	Ledentu	—	5,894	112	Chiefly bac dys 8 cases amoeb	Civil population
	1928	Robac J	—	—	—	Chiefly Shiga and Flexner	Previously dys had been considered amoebic in type
RHODESIA	1931	—	Roan Antelope and N'khana Mines	71 Europeans 115 Natives	13 27	Amoeb and bac dys amoeb more prevalent	Mine workers
BASUTOLAND	1931	Official statistics	—	161	114	Bac dys	Specially fatal in Lerer Colony (18 deaths)
UNION OF S AFRICA AND S W AFRICA	1928-31	Official statistics	—	—	3 per 1,000	—	Population of 7,000 miners
	1930	Brink C D Camp Lell W Mac Padyen J A and Classens J D	—	—	—	Amoebiasis 4½ times as prevalent as bac dys	—
	1929	Fischer W O	Rand	—	—	—	In 1402 post mortems on native miners, amoebic dys lesions found in only 15 cases liver abscesses in 4
BELGIAN CONGO	1930	Official statistics	—	126 Europeans 3,113 Natives	— —	10 bac dys, 110 amoeb 47 bac dys, 3,039 amoeb	— —



COUNTRY	DATE	OBSERVER	PLACE OF EPIDEMIC	NUMBER OF CASES	DEATHS	TYPE OF DYSENTERY	TYPE OF PATHOGEN (Age, Army, Prison, etc.)
BELGIAN CONGO	1930	Official statistics Pergler J. V. and Van Riel, J. Official statistics Van Hoof, L.	Kasi provinces Eastern prov- inces Katanga, Panda- —	6-8% of pop 12,000 Natives 462 Natives —	40%	Shiga predominant	—
	1930				—	Shiga predominant	—
	1925				90	Bac dys	Sporadic outbreaks co- inciding with famine
FRENCH CONGO	1928	—	—	155	—	All types 21.9%	—
NIGERIA	1925	Connell A. and Smith E. C.	—	—	—	—	Reported autopsy find- ings of what they considered to be first case of bac dys More accurate records 1929-31 Amœbic form predominates
	1930	Official statistics	—	218 Europeans 334 Natives	—	164 amœb 32 bac 2893 amœb 28 bac	—
GOLD COAST	1931	Young J. A.	—	438	—	128 bac dys 22 Flexner	—
	1929-31	Official statistics	—	3,968 Natives	77%	20.3% bac dys	Amœbic form pre- dominates
LIBERIA	1930	Strong R. P.	—	—	—	Amœb and bac dys	Dysentery rarer in Li- beria than in many tropical countries
SINRA LÉON	1930	Official statistics	—	777	—	4 cases of bac dys	No full time pathologist Identification un- certain

TABLE X (Cont.)

COUNTRY	DATE	OBSERVER	PLACE OF EPIDEMIC	NUMBER OF CASES	DEATHS	TYPE OF DYSENTERY	TYPE OF EPIDEMIC (Age, Army, Prison, etc.)
GAMBIA	1929-31	Official statistics	—	63	—	4 cases of bac dys	No full time pathologist Identification un- certain
FRENCH W AFRICA—							
Senegal	1930	Official statistics	—	1,020	—	Bac dys	—
Mauritania	1930	Official statistics	—	667	—	Bac dys.	—
French Sudan	1930	Official statistics	—	281	—	Bac dys	—
Ivory Coast	1930	Official statistics	—	6,170	—	Bac dys	Dock workers
ALGERIA AND TUNIS	1930	—	—	—	—	0.19 per 1,000 bac dys, 0.9 per 1,000 ameb dys more prev in Tunis	Cyrian pop. dys. low, military pop. higher
N AMERICA —							
CANADA	—	—	—	—	—	Bac dys predom- inates	Relatively rare
U.S.A. (NORTH)	—	—	—	—	—	—	Relatively rare. Only epidemic cases of ameb bio dys. are found
Boston	1930	—	United Fruit Co.	30	—	Sonne	Children
California	1928	Stanley, L. L., Garfinkle, F. E., and Goddard, W. P.	—	82	8	Flewner	Prison
	1928	Lommel, J.	—	946	—	—	—
	1928	—	—	—	—	Sonne	Child (mild dys.)

COUNTRY	DATE	OBSERVER	PLACE OF EPIDEMIC	NUMBER OF CASES	DEATHS	TYPE OF DYSENTERY	TYPE OF EPIDEMIC (Agt, Army, Prison, etc.)
USA (South)	1930 1931 1932	Melency, H E Milam, D F Melency, H F Bishop, F I, and Leathers W S	—	—	—	Bac dys rare	Few statistics available
CENTRAL AMERICA							
BRITISH HONDURAS	1930-31	Official statistics	—	166	—	—	Hospital No differ entiation —
COSTA RICA	1932	—	—	907	70	Amoeb	—
PANAMA	1931	—	—	16302 Hosp cases	—	Bac dys 4 cases majority amoeb	—
LEeward Is <i>Antigua</i> <i>Dominica</i> <i>St Christopher</i> <i>St John</i>	1931	Official statistics	—	—	106	Infection not recog nized Consu ered amoebiasis	Children
WINDWARD Is	1928-30	—	Grenada	164-34 and 10 respectively	—	—	—
BAHAMAS	1930	—	—	—	—	Bac dys no amoeb	—
BARBADOS	1931	—	—	—	107	Bac dys no amoeb	49 deaths in children under 5
JAMAICA	1931	—	Kingston (Hosp)	16	3	No mention of amoebiasis	—

TABLE X (Cont.)

COUNTRY	DATE	OBSERVER	PLACE OF EPIDEMIC	NUMBER OF CASES	DEATHS	TYPE OF DYSENTERY	TYPE OF EPIDEMIC (Age, Army, Prison, etc.)
FRIDAYAD	1931	—	Coura District	322 (Hosp.)	—	20 cases recognized as bac dys	—
HAITI	1930	—	—	—	—	—	Information unsatisfactory
PUERTO RICO	1928-29	—	—	6 473	717	Bac exam in 137 cases only Flexner's bac found	—
S AMERICA BRITISH GUIANA	1919-31	—	—	200 per ann	10-19 per ann	No differentiation recorded	Records unsatisfactory
DUTCH GUIANA	—	Flu P C	Surinam	—	—	Amoeb rare Bac dys only in small epidemics	Records unsatisfactory
BRAZIL	1927	Bernd M and Bachman	Northern provinces	—	—	Amoebiasis	—
	1929	Vieira P B	Southern provinces	—	—	Bac dys	—
	1931	De Assis and Mendes	Rio de Janeiro	153	—	Flexner predominant (Flexner 74.5%, Shiga 20.9%), Sonne Majority bac dys	In 1929 epidemic, chiefly children
ARGENTINE	1930	De Mendonca	São Paulo	—	—	—	—
		Public Health Reports	Buenos Aires	804	—	Bac dys 27.4%, Flexner, 73.6%, Shiga, 21.0%, Sonne, also found	Civil population

COUNTRY	DATE	OBSERVER	PLACES OF EPIDEMIO	NUMBERS OF CASES	DEATHS	TYPE OF DYSENTERY	TYPE OF EPIDEMIC (Age, Army Prison etc.)
CHILE & PERU	1932	Garcés, C.	—	—	200-300 per ann	Amoeb in adults bac dys in children	Records few
AUSTRALIA	1931	Brown I and Hickey G V	—	—	—	Bac dys except in N territory Sporadic cases of amoeb only	Incidence low
	1931	Burnell T M McKee M and Wood I J	—	—	95	56 deaths bac dys Maj of bac dys cases in children Flexner some Sonne	Civil population
NEW ZEALAND	1932	Official statistics	—	45	10	Bac dys	Civil population
OCEANIA NEW GUINEA NEW BRITAIN	—	Official statistics	—	—	—	Mostly bac dys but some amoeb	Liquidum dys
	1932	Official statistics	—	471	138	Bac dys	—
PAPOA	1928	Crichlow N	—	—	Heavy	Bac dys	Epidemic and epidemic
NEW HEBRIDES NEW CALEDONIA	1930	Official statistics	—	—	—	Bac dys (amoeb 97%)	—
Fiji Islands	1912 1929-30 1931	Official statistics (Bahr P H) Official statistics	—	608 (Hosp)	—	Bac dys Shiga and Flexner Shiga predominant Shiga predominant	Epidemic (amoebasis epidemic) Epidemic 1929-30 Similar outbreak

TABLE X (Cont)

COUNTRY	DATE	OBSERVER	PLACE OF EPIDEMIC	NUMBER OF CASES	DEATHS	TYPE OF DYSENTERY	TYPE OF EPIDEMIC (Age, Army, Prison, etc)
GILBERT AND ELLIS I	1930-1	— Official statistics	Funafuti W Samoa	— —	— —	Bac dys Bac dys due to Shiga Bac. dys	Civil population —
HAWAIIAN I	1932	—	Tonga Isl	2	—	Bac dys rare	—
ASIA—							
PALESTINE	1919	Manson Bahr P H	—	—	—	Bac dys preva lent. Some ameb. in native troops	Expeditionary Force Seasonal curve
	1927	Kluger I J and Westman I	—	—	—	Bac dys out of 65% stools 35% bac dys	Civil population
	1927	Oltzki L and Reich K	—	—	—	Bac dys ameb in summer	Seasonal epidemic peaks spring and autumn 20% in children 6 mths 2 yrs
	1927 1931	Official statistics	— —	1 782 297	— —	25% bac origin Bac dys	—
TRANSJORDANIA	1931	Official statistics	—	28 (examd)	—	20 bac dys	—
SYRIA	1931	—	—	—	—	Bac dys rare	Spore like
IRAQ	1917 18	Ledingham J C G	Mesopotamia	715	—	Shiga 40 30% lex ner 54 7%	Spring and autumn Incidence greater in Brit than in Indian troops —
	1927	Skelton D S Mal colm J W and Joy I R	Mosul area	—	—	Bac dys	—
	1925-26	League of Nations	—	54 161	—	Diarr and dys	Civil population

COUNTRY	DATE	OBSERVER	PLACE OF EPIDEMIC	NUMBER OF CASES	DEATHS	TYPE OF DISEASE	TYPE OF EPIDEMIC (Age, Army, Prison, etc)
INDIA	1930	League of Nations	—	—	—	64.6% bac dys amceb 8.4%, Ind, 15.6%, Brit, Flexner, 77.6%, 15.7%, Sonne 2.2%, 80% bac dys, mostly Shiga, 30% amceb	Brit and Indian troops
	1927	Large, D T M	Lahore	—	—	479 protozoal, 16 bac	—
	1922	Official statistics (Army)	—	373	—	303 protozoal, 1 bac 9 unclassified	—
	1923	Cunningham J Official statistics	E Bengal Madras Presi dency	—	—	86% bac dys	Prisons
	1920-23	Acton H W and Knowles R	Calcutta	—	—	86% bac dys	Prisons (Majlah Rising)
	—	—	—	—	—	Bac dys amceb 5 1	—
CEYLON	1929	Colonial Office Re ports	—	5 909	—	4,478 (75.8%) amceb 1,429 (24.2%) bac dys	Civil population
	1929	Official statistics	W Province	10 365 out pts 7,242 in pts	3 616 1 032	Majesty Flexner	—
	1931	—	—	489	—	383 (78.7%) bac dys	Sporadic Higher in W Province
SIAM	1925-26	—	—	6 016	—	Of 1,847 stools exam 28 amceb	—
MALAYA	1910	Fraser H	—	—	—	—	—
	1924	Fletcher, W, and Jeppa, W	—	—	—	80% bac dys	Bac and amceb equal in Fed Malay States

TABLE X (Cont.)

COUNTRY	DATE	OBSERVER	PLACE OF EPIDEMIC	NUMBER OF CASES	DEATHS	TYPE OF DYSENTERY	TYPE OF EPIDEMIC (Age, Army, Prison, etc.)
MALAYA	1930	Official statistics	Federated Malay States	1,735	—	868 bac, 869 amceb	—
	1930	"	Kedah	250	—	90 bac, 160 amceb	—
	1930	"	Kelantan	54	—	6 bac, 48 amceb	—
	1930	"	Trengganu	37 Hosp	—	4 bac, 29 amceb, 4 undefined	—
STRAITS SETTLEMENTS	1929	Official statistics	—	1,167 Hosp	—	290 bac, 531 amceb	Civil population
	1931	"	—	—	249	117 bac, 103 amceb 23 undefined	"
	—	"	Singapore	234	—	10 bac, Shiga 3, Flexner 16, Hiss and Russell 6	"
DUTCH INDIES	1919	Baerman, G	—	0.8 per 1,000	—	Amceb	Plantation coolies
	1925	"	—	0.7 per 1,000	—	Bac dys	"
	1927	Wolf, J W	Sumatra	—	—	—	Increasing import of bac. dys as factor
	—	—	Java and Celebes	—	—	Bac dys noted	—
	1932	"	Java and Madura	698	81	Amceb dys endemic	—
	—	"	Celebes	135	—	—	—
	—	"	Timor	40	—	—	—
BORNEO	1931	—	Kuching (Sarawak)	615	36	Bac dys	Population of 24,000
	—	—	Brunei	9,947 197 (Hosp)	164	Bac dys 9 bac dys, 3 amceb	—



COUNTRY	DATE	OBSERVER	PLACE OF EPIDEMIC	NUMBER OF CASES	DEATHS	TYPE OF DYSENTERY	TYPE OF EPIDEMIC (Ags, Army, Prison, etc.)
PHILIPPINE I	1926	Wilson I. and Quason, J. O.	—	136	91 0°	Flexner bac	May October
	1928		—	11 056	4 532	2 074 ameb, 1 987 bac dys	—
	1928	Mendoza M. P.	Manila	—	132	14 ameb, 50 bac dys	3 epidemics frequent in rainy season
	1929	Cajigas G.	Manila	200	76	Shiga 1 k xner & Moran's	Children chiefly
CHINA	1931		Hong Kong	115 Govt Hosp 798 Chinese Hosp	3 40 ameb 10 bac dys	57 ameb 47 bac dys 146 ameb 48 bac dys Flexner predom Shiga rare	Civil population
	1912	—	Shanghai	90 ameb 122 bac dys	5 ameb 8 bac dys		1 foreigners
	1931	—		—	—	600 stools dys Ma jority 1 k xner or Sonne 72 Shiga	Bac dys more frequent in towns
	—	—	Central China	—	—	Amoebas chiefly	—
	1930	Smiley H. J. and Lee S. W.	Leiyang	—	—	Bac dys	—
	—	—	—	38	—	28 bac dys, 7 ameb Several mixed	Complicating periton
	—	—	S. Manchuria	—	—	Bac dys to ameb 14 1	—
	—	—	—	—	—	—	—
	—	—	—	—	—	—	—
	—	—	—	—	—	—	—

TABLE X (Cont.)

COUNTRY	DATE	OBSERVER	PLACE OF EPIDEMIO	NUMBER OF CASES	DEATHS	TYPE OF DYSENTERY	TYPE OF EPIDEMIO (Age, Army, Prison, etc.)
CHINA	1928	Hoshigaki S	Dairen	1 220	54 90°	1,114 Japanese, 106 Chinese Hiss and Russell 46 10° Shiga 39 30° Flexner 5 60° Others 9 10° —	Chinese mortality three times as high as Japanese
	1927	—	—	—	24 40° (Shiga) 39 40° (Others)	—	Toxic symptoms less marked in Shiga
	1928	Tsuchiya, K and Nagata S	—	—	—	—	Shiga commoner in chil- dren over 7
JAPAN	1929	—	—	—	3 160	Bac dys predom- inant	Acute type in children under 5 (Eltz)
	—	—	—	—	10 261 (Eltz)	—	Female deaths exceed males
	1927 1926	Mitsuhashi C Sasaki, R	— —	35 30	— —	Bac dys, Flexner chiefly	Incidence higher, July- Sept Women's School Fulminating cases

## CHAPTER XI

### AMŒBIASIS (*continued*) PATHOLOGY, MORBID ANATOMY, SYMPTOMATOLOGY AND COMPLICATIONS

THE pathological appearances of intestinal amœbiasis so intimately connected with the activities of *E. histolytica* naturally vary enormously in their extent according to the severity of the infection and resisting power of the host. As far as is at present understood the mature living cysts of *E. histolytica* when swallowed pass into the stomach and are not affected by the gastric juices. It is not until they



*Phil p Manson Bahr*

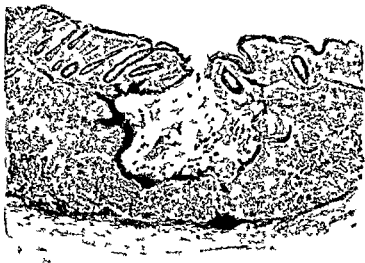
Fig 17 — Microscopic section of the large intestine showing the entrance of large tissue invading forms from the mucus investing the mucosa and penetrating the crypts of Lieberkuhn

reach the small intestine that the cyst walls are dissolved and the liberated amœbæ pass with the intestinal contents into the large intestine where they establish themselves. Amœbic dysentery is thus a disease of the large intestine but occasionally in very acute cases it may attack the small gut also (A. G. Biggam 1930).

The young amœbæ first attack the mucous membrane destroying the cells of the columnar epithelium. They then pass down the crypts

of Laoberkühn and penetrating the basement membrane gain entrance to the submucosa. Here they attack and invade the tissues both by their own activities and by means of a powerful cytolytic ferment as was shown by C. Craig (1927) (Fig. 17).

Soon by active proliferation nests of amœbæ form which destroy the tissues in their vicinity very rapidly so that they come to lie in a pool of cytolysed tissues which affords a rich source of nourishment and there they multiply rapidly. The amœbæ engulf red blood corpuscles, leucocytes and the remnants of tissue cells. (This description agrees in detail with that of W. J. Councilman and H. A. Lafleur (1891).



P. H. M. B.

Fig. 18—Section through flask shaped ulcer showing amœbæ in situ.

(After Craig from American Army Museum Collection.)

The earliest lesions seen on the mucous surface are yellow papular elevations containing viscid pus communicating with the submucosa. By studying the genesis of amœbic ulcers by sigmoidoscopy it has been ascertained that initially the ulcers are often very small and take the form of punctiform depressions of the mucous membrane. This submucosal lesion spreads and when sufficient pus has collected it bursts into the lumen of the bowel producing an ulcer with a narrow neck, a broad base and an undermined edge which when seen in vertical section assumes the shape of a flask (flask shaped ulcer) or which if it spreads on the surface in a horizontal direction resembles a buttonhole—*bouton en chemise*. (Fig. 18).

E. C. Faust (1941) in a series of 202 post mortem examinations on accident cases in New Orleans found 6.44 per cent infected and was

able to demonstrate *Entamoeba histolytica* in the lesions which were of a mild type, consisting of almost inconspicuous pin point ulcers, shallow craters and very superficial erosions, without evidences of inflammation. The amoebic processes suggested a milder much less advanced pathology than usually described, demonstrating a better balance between host tissue and parasite.

Deep ulcers usually have swollen or raised edges and are surrounded by numerous hæmorrhages. The smallest take the form of granular patches on the mucous membrane which are very difficult to see except with a magnifying lens. These ulcerations assume different appearances according to the reaction of the tissues. As a general rule, in contradistinction to the bacillary form the mucous membrane intervening between individual ulcerations is normal in colour and in texture. When large necrotic sloughs form at the base of amoebic ulcers they assume a filamentous appearance projecting into the lumen of the bowel, roughly resembling a tuft of hairs (Plate III 1 facing p 50). They have been termed 'dyak hair sloughs' by W. Fletcher and M. W. Jepps (1924), from their resemblance to the tufts of black hair which the head hunters of Borneo were wont to wear on their sword hilts. In less severe cases the ulcers are more superficial and the whole colon may be covered with what are appropriately termed 'sea anemone ulcers', with rounded raised margins and white fluffy bases. Solitary ulcers are sometimes seen, and may be found even in the rectum, or again the whole surface of the colon may be covered with a stringy black exudate resembling seaweed. Usually the walls of the cæcum and the ascending colon are attenuated and dilated, and sometimes the portions of the bowel between the ulcerations become stretched and attenuated, forming sacculations (Plate VII). Where the dysentery has been of long duration the walls of the large intestine are much thickened and fibrosed and the appendices epiploicæ greatly enlarged. Areas of hypertrophy may alternate with dilations so that it is easily appreciated that chronic amoebiasis may interfere considerably with the physiological functions of the bowel.

It will readily be appreciated that amoebic ulceration does not resemble the catarrhal inflammation of bacillary dysentery, though it must be admitted that it is sometimes difficult to determine the nature of lesions in the rectum, especially when chronic ulcers have become secondarily infected. Chronic bacillary and amoebic lesions may co-exist, especially in natives. It may be said that scattered ulcers with shallow undermined edges and bases formed of granulation tissue are of bacillary origin. By employing appropriate technique there is no difficulty in isolating the dysentery bacillus from these lesions, and in amoebic ulcers, amoebæ may usually be demonstrated. It is interesting to note that healed amoebic ulcers take the form of smooth, depressed non-pigmented scars while those of bacillary origin are pigmented and extremely friable.

The character of the stool depends to a great extent upon the size and

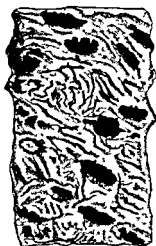
nature of amœbic lesions When much necrotic tissue is present the faeces are foul and contain greenish sloughs

Amœbic lesions are especially abundant in certain portions of the bowel being as a rule most extensive in the neighbourhood of the flexures When they are very numerous the mucous membrane of the large intestine may be so undermined and burrowed by ulcers that the surface may resemble a tangle of seaweed (Plate VII 3)

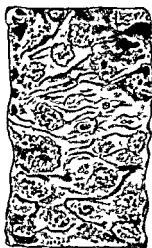
A W Sellards and L Leiva (1923) have shown that when the cæcum is exposed and material directly introduced into the lumen of the bowel infection takes place with surprising regularity Whether introduced into the cæcum or *via* the rectum, the initial lesions occur in the extreme lower part of the bowel Stasis occurring in the large bowel certainly affords an opportunity for amœbæ to gain a foothold and is a factor determining the location of the initial lesion The subsequent dissemination of the lesions indicates that there are no pronounced differences in the susceptibility of various areas of the colon In dogs however E C Faust and E S Kagy found that the cæcum usually constituted the earliest site of an amœbic attack

The most extensive experimental investigations on the pathology of amœbiasis in cats and dogs and its bearing upon the pathological histology of the disease in man are those of O Wagner and R Bieling (1935) who found that following both rectal and oral administration of infected material two points of the large intestine are first attacked — namely the lower part of the large intestine immediately above the anal ring and the region just below the ileo cæcal valve The amœbæ here enter the tissue in one of three ways passing directly into the connective tissue into the crypts or into the lymph channels whence they migrate to the lymph follicles and the submucosa The intestinal mucosa responds to the invasion by an increased production of mucus which when mixed with blood forms an excellent medium for the development of amœbæ on the surface of the intestine

As a rule ulcers in the rectum are the most minute hence the necessity of being able to recognize them by the sigmoidoscope The most extensive work on the distribution of amœbic lesions in the bowel is that by H C Clark in 1924 In 186 fatal cases examined postmortem the lesions were scattered throughout the colon in 61 per cent and involved isolated areas alone in 34 per cent affecting in order of frequency the cæcum ascending colon iliac colon rectum and hepatic flexure in ten cases (5 per cent) no ulcers but only scars were found these being cases of secondary amœbiasis with infection of other organs (Fig 19) As has been already pointed out, stasis is of great importance in intestinal amœbiasis and as might be expected it is at the sites where this is greatest that there is a special tendency for the amœbæ to invade the bowel Of interest was the fact that the appendix was affected in 41 per cent of cases and in 9.2 per cent perforation or abscess formation had occurred it being proved by microscopic section in six cases that there were extensive



1, "Dyak-hair" sloughs



2, "Sea-anemone" ulcers



3, "Seaweed" sloughs



4, Typical punched-out ulcers with thinning and ballooning of intestinal walls

## PATHOLOGY OF THE COLON IN AMÆBIC DYSENTERY

(Drawn by P H Manson Bahr, after W Fletcher and M W Jepps)

1 Amœbic ulceration of descending colon  
(proved by sigmoidoscopy and faeces examina-  
tion) Note slight filling defect of cæcum  
(Dr Carmichael Low's case)

Pl. 8 Dr G. MacKer Cordner

2 Amœbiasis of descending colon the same  
case four years later showing formation of  
pericolic abscess

## AMŒBIASIS OF THE DESCENDING COLON

PLATE VIII



amoebic lesions. Wherever there was amoebic ulceration of the cæcum the appendix also was involved. It must be pointed out that the frequency of appendix lesions in Clark's series appears to be extraordinarily high, most of his autopsies were made in negroes among whom the incidence of appendix lesions may be higher than in other races, since they possess, as a rule, large appendices with a patent lumen.

The distribution of amoebic lesions (primary amoebiasis) in Clark's 186 cases can be best presented in tabular form (Table XI, *overleaf*).

The post mortem appearances of amoebic dysentery are naturally

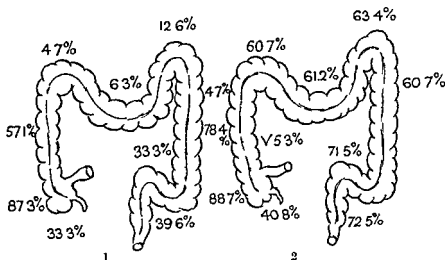


Fig 19—Diagrams showing distribution of amoebic lesions in the appendix, colon and rectum (After H C Clark 1924)

1, Regional distribution in 186 cases. 2 in 63 cases. Note the incidence of lesions in the cæcum, sigmoid and appendix. The dependent portions represent the regions where the greatest stasis exists in the colon and which afford a resting place for the development of the amoebæ. The primary locations are found in the cæcum, ascending colon, rectum, sigmoid and appendix.

complicated if perforation of the intestinal ulcers should have occurred. This is one of the accidents in intestinal amoebiasis; hæmorrhage is another. In Clark's series, perforations of the ulcers were noted in the cæcum in three cases, in the appendix in three, in the rectum and sigmoid in three also, and in the splenic flexure in one case, while in one instance a fæcal fistula and fistula in-ano were proved to be of amoebic origin. Localized peritoneal abscesses, formed by walling off of the peritoneum in the neighbourhood of perforated amoebic ulcers, have also been noted.

Where the blood supply of the bowel has been severely interfered with through thrombosis of the submucous veins and secondary bacterial invasion, extensive gangrene of the mucosa may ensue, followed by sloughing. Large areas of the bowel may be involved in

TABLE XI

<i>Distribution</i>	<i>Cases</i>
<i>Entire colon</i>	55
Entire colon and ileo caecal valve	3
Entire colon and appendix	48
Entire colon and appendix and ileo caecal valve	7
Cæcum and ascending colon	24
Cæcum, ascending colon, and appendix	9
Cæcum, rectum, and sigmoid	8
Cæcum, rectum, sigmoid, and appendix	6
No primary lesions found in the intestine or appendix	7
Scar or almost healed lesions in the colon	3
Appendix, cæcum, splenic flexure, and rectum	2
<i>Rectum</i>	2
Rectum and sigmoid	2
Appendix, cæcum, both flexures, and rectum	1
Rectum, sigmoid, and splenic flexure	1
Appendix, cæcum and splenic flexure	1
Cæcum and ascending and transverse colon	1
Appendix, cæcum, and ascending and transverse colon	1
Rectum, sigmoid, and descending colon	1
Rectum, sigmoid, splenic flexure, and cæcum	1
<i>Splenic flexure and descending colon</i>	1
Appendix cæcum, ascending and transverse colon and hepatic flexure	1
Rectum, sigmoid, descending colon, transverse colon, both flexures	1

this process and the result is invariably fatal. Rarely, the small intestine may be attacked, and Clark records that the lower end of the ileum and the ileo caecal valve were involved by amœbic ulceration in 5 per cent of cases. This observation has been confirmed by A. G. Biggam.

Apart from the appearances of the bowel there is little in the post mortem appearances of intestinal amœbiasis that is characteristic, the cadaver shows few signs of toxic absorption and the viscera few changes.

**Histopathology.**—The lesions caused by the amœbæ are followed by characteristic reactions in the tissues. First, the smaller capillaries show signs of stasis and finally become thrombosed, the resulting exudation of fluid producing œdema and coagulation necrosis. The inflammatory changes in the surrounding tissues are not accompanied by outpouring of a large number of inflammatory cells and leucocytes such as is generally seen in bacillary lesions but when present this may be taken as evidence of a secondary bacterial infection. The amœbæ are specially apt to invade the walls of thrombosed vessels and may be recognized in the coagulum, and it is no doubt, by this means that they gain access to the portal circulation and eventually reach the liver (Fig. 20). The necrotic tissue produced by amœbic infection has a glassy gelatinous appearance which somewhat resembles Zenker's necrosis in typhoid and diphtheria. As a rule, this does not extend

deeper than the submucous layer but in some cases the amœbæ may destroy the muscular layers and finally reach the peritoneal coat.

The necrotic tissue in the cavity of the ulcer consists of gelatinous coagulum containing cells in all stages of destruction and frequently masses of extruded nuclei. histiocytes (macrophages) being commonly encountered. D. L. Martin (1930) points out that, beyond the boundaries of the cellular infiltration the lymph vessels may be found dilated, with their contents coagulated.

When the amœbæ have penetrated the fundi of the glands they



Fig. 20—Microscopic section through the submucosa showing three amœbæ (*E. histolytica*) within the lumen of a vein

break through the basement membrane and penetrate the muscularis mucosæ, either through tissue spaces or via the lymph or blood vessels (Fig. 21). Arrived in the submucosa they spread out causing œdema with the result that the submucosa often becomes infiltrated to several times its normal thickness.

At first there is little or no response on the part of the host but when bacteria gain entrance to the tissues, marked cellular reaction occurs and the submucosal lesion takes on the appearance of a pyogenic abscess with few visible amœbæ. Should the lymphatics of the submucosa have been opened up by necrosis they may become filled with necrotic cells and bacteria—more strikingly in the artificially produced disease in kittens than in man. Although amœbæ enter the lymph vessels and are undoubtedly carried to the mesenteric lymph glands lesions are practically unknown (H. E. Meleney).

Should the patient be a carrier of the cysts of *E. histolytica*, there are a number of ulcers in the bowel, it appears possible, from the observation of W E Musgrave, G B Birtlett, and other pathologists, that a considerable degree of ulceration may be compatible with good health and may exist in the absence of dysenteric symptoms

The healing of amœbic ulcers is important and it is necessary to be

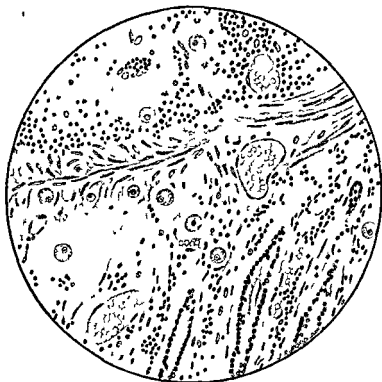


Fig 21 —Section through base of amœbic ulcer showing *E. histolytica* in the tissues (C M Wenyon)

familiar with their appearances. When separation of the sloughs has taken place, granulation tissue forms on the surface and floor of the ulcerated area and a parchment like slate grey scar results. Regeneration of the mucous membrane, even with extensive ulceration is much more rapid and effective than has been generally supposed.

**Pathology of amœbiasis in experimental animals**—It has become evident that care must be exercised in drawing conclusions from a study of the pathological conditions in experimental animals. In kittens injection leads to a very acute and rapidly fatal amœbic dysentery while in the dog it is invariably of the chronic type.

C W Rees (1929) found that, of forty nine kittens which were inoculated with cultures of *E histolytica* directly into the intestines after laparotomy, twenty three developed lesions, while of thirty seven infected intrarectally fifteen developed similar lesions. In kittens directly inoculated after laparotomy, ulcerations could not be found till forty hours had elapsed, but lesions were found after ninety hours, especially near the ileo caecal valve. R W Nauss and I Rappaport (1940) have made an important observation that invasiveness of *E histolytica* for the intestinal mucosa of kittens is increased by the irritant action of croton oil and that of certain bacteria associated with cultures of *E histolytica*.

D L Martin (1930) in a study of infection induced by rectal injections, found that the primary lesion took the form of necrosis of the superficial epithelium of the intestine, and concluded that the lesions are produced by cytotoxicity. He thought that mechanical penetration of the tissues by the entamoebae had no physiological effect as far as the production of lesions was concerned, but that bacteria play an important part, especially as secondary invaders. Natural healing of the lesions in the cat apparently does not take place. Amoebic abscess of the liver can arise in cats as early as four days after the appearance of dysenteric symptoms in others as late as two or three weeks after.

Experimental amoebiasis in the dog is a much more chronic disease. S T Darling described a case of spontaneous amoebiasis in a dog and found that the whole colon was the seat of minute punctiform red erosions of the mucosa, covered with flakes of mucus. The amoebae had also produced ulceration of the ileum.

The exact part played by the *E histolytica* in the production of the microscopic pathology of intestinal amoebiasis has been studied by E C Faust and E S Kagy in the experimentally produced disease in the dog in which the pathology is apparently very similar to that of man. Within seventy two hours of the introduction of infective material containing *E histolytica* into the large intestine of dogs a superficial inflammation and lysis of the inter glandular layers appears, with involvement of the crypts. The amoebae then penetrate the mucous membrane either between the glands or by passing through them, and soon colonies could be observed between the base of the gland and the muscularis mucosae. Later still the amoebae were found in the submucosa, where they produced flask shaped ulcers.

It is doubtful whether experimental amoebiasis has been produced in the rabbit or guinea pig, but, according to D L Martin rats occasionally seem to be susceptible. Natural amoebic infections are rare in animals (see Appendix) though monkeys in captivity contract it readily. U Mello (1923) described a case of amoebic hepatic abscess with ulceration of the appendix in an orang utan, and E W Sudley (1924) found *E histolytica* cysts in the faeces of a chimpanzee, and P Hegner (1930) in Philippine monkeys. C Dobell (1926) has cultivated four species of amoebae from monkeys and he believes that *E nuttalli* is indistinguishable from *E histolytica*. D Hunter (1936) has reported a case in a dog in the Dutch East Indies, and Z Morcos other instances in Egypt.

#### SYMPTOMATOLOGY OF AMOEBIC DYSENTERY

Like other protozoal diseases in man, amoebic dysentery exhibits the most varied clinical pictures. Although acute and rapidly fatal cases undoubtedly do occur, yet they must be considered exceptional. It has

already been pointed out that, on the whole, *Entamoeba histolytica* endeavours to subsist on the best terms with its human host, therefore amœbic infection in man results, as a rule, in a long drawn out chronic disease. Even when symptoms of dysentery are obvious, infection is compatible with fairly good health. Cases are not uncommon in which the patient, although exhibiting continuous dysenteric symptoms with passage of blood and mucus in the stools, nevertheless leads an active and useful life without any appreciable loss of weight. W M James of Panama describes the varied nature of amœbiasis as follows. Like other protozoal infections, that of amœbiasis follows a protean course. It may be fatal in a short time. It may become chronic with alternating periods of dysentery and constipation or with passage of unformed stools. It may be mild and cause little discomfort. So extremely variable are the symptoms of this infection that it may simulate almost any gastro intestinal trouble. In chronic amœbic dysentery emaciation is the exception rather than the rule, but it occurs usually in the acute stage. When death occurs it is the result of an accident, for example, of perforation of an amœbic ulcer with resulting general peritonitis, or of the opening up of some large blood vessel in the intestinal coat, death then being due to uncontrollable hæmorrhage.

It is difficult to define the position of carriers in the symptomatology of the disease. It has been pointed out that if they are closely watched and studied over a period of years some variations from normal health may be detected, and it is probable that if they could be observed throughout life they would be found to suffer periodically from mild dysenteric symptoms. Furthermore it is urged that there is the ever present liability to hepatic amœbiasis (see p 201) but, most important of all they do constitute a potential source of danger to others.

It is possible to divide sufferers from primary intestinal amœbiasis into four classes the mild the acute the fulminating and the chronic, the great majority of cases being included in the last category.

**Incubation period**—The incubation period of intestinal amœbiasis is one of considerable length. We owe our knowledge of this subject to the work of F L Walker and A W Sellards in 1918. They experimented with twenty volunteers by feeding them with amœbic material by the mouth. Of these twenty seventeen became parasitized after the first feeding the average period before the organisms appeared in the faeces being nine days. Of the eighteen who eventually became thus experimentally parasitized four, or 22.2 per cent developed symptoms of amœbic dysentery. The incubation period of dysentery in these experimental infections was on an average 61.8 days. In the Chicago outbreak of 1933 the incubation period was estimated at 7-15 days even up to 74-77 days symptoms occasionally appeared within one week, and in a few cases not for three or four months.

**Duration of infection**—Intestinal amœbiasis is undoubtedly one of the most persistent of all protozoal infections. It is probable that a

person, when once heavily infected, remains so for life unless treated. In the author's series of cases, in four patients the symptoms had persisted for twenty and in one, for thirty years. C. Dobell and A. C. Stevenson (1918) concluded that infection might persist for sixteen to thirty four years. Until recently it was comparatively common to find in England, uncured, ex soldiers who had become infected during military service in India in the frontier wars of the last century. Infections dating from the South African War of 1899-1901 were also encountered. The author has recorded one case in a British officer who developed an acute attack of amœbic dysentery, which responded successfully to treatment, after he had resided seventeen years in England without experiencing any symptoms of this disease. A case of amœbic ulceration of the rectum has also been seen in an ex soldier in whom symptoms of bleeding were first noted in 1937, i.e. twenty years after he had contracted dysentery on the Somme in 1917. Furthermore, the symptoms of amœbic dysentery may vanish temporarily with apparent restoration of health, and these quiescent periods may last for two or three years. The author treated in 1937, an ex soldier from India who suffered from an acute exacerbation of dysentery after a quiescent period of eight years, and in 1941 an erstwhile official of the Indian Forest Service who suffered from a recrudescence of amœbic dysentery thirty one years after abscess of the liver.

One of the difficulties in describing the symptomatology of amœbic dysentery is the number of other intestinal conditions which it may simulate. There is hardly an affection of a single abdominal organ for which it may not be mistaken. It has been pointed out that any diagnosis, from simple indigestion to cancer, is compatible with the very varied symptomatology of intestinal amœbiasis.

The onset is seldom sudden, most usually it is gradual and progressive, and the patient, although inconvenienced, endeavours to carry on his work. Very often it commences as a mild *diarrhœa*, and it is not until this has lasted several days that blood and mucus appear in the stool. There is a large class of cases which may be labelled 'amœbic diarrhœa,' because, in the whole course of the illness, none of the more familiar symptoms of dysentery make their appearance. A feature of the diarrhœa in amœbic dysentery, one it has in common with other serious abdominal diseases, notably carcinoma, is the alternation of diarrhœa and constipation. Intense abdominal symptoms, such as excruciating pain, colic and tenesmus, which characterize bacillary disease, are generally absent. There is usually considerable abdominal discomfort rather than pain, and the patient would probably be most accurately described as suffering from an 'uncomfortable abdomen,' or a 'growling belly.' In contradistinction to bacillary dysentery, tenesmus is rare and was noted only in 7 out of the author's 535 cases.

*Fever*, as a rule, is not a feature of the amœbic, as it is of the bacillary

form of dysentery, except in the presence of some complication such as hepatitis. Exceptional cases with hectic fever have, it is true, been observed from time to time, but these are probably due to septic absorption from the extensive intestinal ulceration.

The author has records of mild pyrexia associated with intestinal amœbiasis in 10 per cent of his cases (1929). Pyrexia is naturally rare but can exist without any involvement of the liver. Occasionally the pyrexia may resemble a malarial attack, and when associated with rigors is probably an instance of periodic invasion of the liver by amœbæ derived from the bowel. (See under Amœbic hepatitis.) Occasionally, continuous pyrexia with intermittent rigors may occur, and may be taken for other infections e.g. a mild attack of typhoid, or there may be persistent low fever without any definite signs, which might suggest tuberculosis though the response of amœbic pyrexia to treatment is peculiarly striking.

The author has described one case of 'amœbic fever' with hectic fever, persisting for sixteen days and of a remittent type which in its clinical features resembled typhoid.

A seaman on arrival from Sierra Leone (July, 1940) had been ill with remittent pyrexia (104° F.) headache, bone pains and signs of toxæmia. Meteorism was prominent, latterly slight diarrhœa had been noted. On one occasion some blood and mucus were seen but no amœbæ were found. Sigmoïdscopy revealed extensive ulceration and in scrape preparations *F. histolytica* were numerous. Response to treatment was dramatic.

It must be remembered that acute cases in the Chicago epidemic of 1933 presented rather unusual features. Many had an acute onset with fever, intense abdominal pain and tenesmus to such a degree as frequently to lead to an erroneous diagnosis of some surgical condition e.g. acute appendicitis or occasionally, malignant disease (8.6 per cent cases). The fatality rate following operation was 40 per cent. The total mortality rate was 7 per cent, and 8.9 per cent developed liver abscess.

The stools in amœbic dysentery are more copious than those of the bacillary form, are nearly always feculent, and are usually much fewer in number, seldom exceeding twelve in the twenty-four hours, more usually they number three or four. They contain much dark and altered blood and have an offensive odour. Usually blood streaked mucus is present as flecks scattered throughout the fecal mass. When the stools are fluid and contain much altered blood with mucus, they are said to resemble anchovy sauce, though it is dangerous to be too dogmatic over the importance of these appearances, but the description may be taken as a practical generalization.

Deeks's observation that in chronic amœbic dysentery a doughy, inelastic skin almost myxœnoid, is often present, appears to be sound.

In acute amœbic dysentery emaciation occurs to a certain degree. In 48 out of 150 cases studied by the author (1929), the loss



of weight recorded was from fourteen to twenty eight pounds in a year, and the greatest loss was of forty two in three months. On the other hand, chronic intestinal amœbiasis interferes so little with nutrition that the body-weight is usually well preserved, and there are records of three cases in which a great increase of weight occurred. Intestinal amœbiasis is thus not incompatible with obesity.

**Pain**—In intestinal amœbiasis subjective pain is, as a rule, localized to certain areas of the large intestine. Usually it is confined to the sigmoid and to the descending colon, or to the right half of the abdomen—to the cæcum and appendix area, and when the pain occurs in this situation the actual outline of the cæcum can be ascertained on palpation. This involvement of the cæcum itself is frequently mistaken for acute appendicitis, and operative measures are consequently undertaken. Amœbic ulceration of the appendix, however, does occur, and perforation of that organ has occasionally been reported (p 154). Moreover, experience shows that an appendicitis of septic origin may co-exist with intestinal amœbiasis (in the author's series (1941) in 5.4 per cent.)

There is one localized pain which, in the author's opinion, has a definite diagnostic value, and that is one elicited on deep pressure in the centre of the sigmoid flexure, at a point opposite the anterior superior spine of the ilium. This might almost be termed the "amœbic sign post" for, as far as observations go, it is not usually found in other forms of colitis (Fig 24, p 178).

Pain may be localized to the centre of the transverse colon or areas of deep tenderness elicited in the epigastrium, where it may suggest some affection of the stomach or gall bladder, when situated at the border of the right rectus muscle, it may suggest cholecystitis. On the other hand, there is a group of cases where colon pain is referred to the lumbar region, suggesting a misdiagnosis of pyelitis or renal calculus.

**Bowel symptoms.**—In 114 out of 150 cases in the author's series (1929) chronic and painless diarrhœa was obvious without blood and mucus in the stool. On the other hand, the anomalous fact emerges that amœbic dysentery is compatible with constipation. Records of not less than eleven such cases have been obtained, and it has been shown that the cure for the constipation in these cases lay in the cure of the amœbic infection.

**Flatulence.**—Flatulence may be a most distressing symptom. It is usually confined to the ascending colon and to the cæcum. Gaseous distension of the cæcum is so frequent in amœbiasis that it may be taken almost as a cardinal sign of the disease, and may be visible on the surface, while on palpation it gives a sensation of fluidity which may be termed "amœbic splash". Flatulence may be so obvious and persistent that the disease may simulate chronic pancreatitis, chronic intestinal obstruction, or, indeed, sprue.

**Dyspepsia.**—Acute dyspepsia, which must be recognized as a feature of amœbiasis, may be the result of flatulence or may represent a reflex pain from the bowel. There is also the possibility that intestinal amœbiasis may be mistaken for duodenal ulcer. This is a condition which rarely arises, but one case was so remarkable that a few details must be given.

A seaman, aged forty five years, was seen in March, 1927. This man had, three years previously, suffered from liver abscess, for which an operation was performed. Subsequently, he suffered from chronic supra umbilical pain, flatulence, and dyspepsia. Quite suddenly he was taken ill with acute abdominal pain, vomited bright blood, and passed a number of black, tarry, melanic stools. Treated on a duodenal regime by alkalis, he failed to improve. Two further hemorrhages took place within the next ten days, and his condition became desperate. The anemia was severe. Motile *E. histolytica* were discovered in a blood clot passed per rectum, and anti amœbic treatment proved successful.

**Palpable abdominal tumours**—An amœbic ulcer, from its site, its general characteristics and the nature of the incessant blood stained discharge, may suggest a malignant growth. An instance of this came under the author's notice in a specimen presented him by J. G. Willmore and Broughton Alcock in 1932. Resection of the colon was undertaken for a mass resembling carcinoma with threatening intestinal obstruction. In sections of the granuloma numerous amœbæ were demonstrated, together with giant cell formation.

M. W. James (1927) has described masses resembling tumours over the cæcal and sigmoid regions with palpable and enlarged mesenteric glands and he has seen them actually melt away under appropriate treatment.

R. F. Vaccarezza and E. Finocchetto (1920) encountered an amœbic inflammatory tumour of the large intestine involving the cæcum and ascending colon, it extended upwards as far as the costal margin and to the middle line, and measured 12 cm. in length by 10 cm. in breadth. Microscopically it had the appearance of a granuloma.

H. Gunn and N. J. Howard (1931) have described three such cases, in which the resemblance to carcinoma was very close. The underlying process consisted of an isolated chronic ulcer with progressive erosion of the bowel wall and, in response to long continued amœbic ulceration and secondary infection, masses of cedematous granulation tissue had formed. This process may affect the entire bowel wall and the neighbouring mesocolic fat, the resulting mass simulating a tumour. Resection of the colon may be necessary, with the aid of emetine treatment. Even then diagnosis may be difficult.

A similar case has been described by C. I. Donald and P. W. Brown (1940). A. M. Haran (1940) investigated one case in which an amœbic granuloma, the size of a peach, had caused intestinal obstruction. The gelatinous consistency of these outgrowths has been emphasized by R. W. Mendelson (1939). R. S. H. Lee (1941) has described a case, in a

Chinese, primarily regarded as epithelioma of the anus for which colostomy had been performed before the discovery of *E. histolytica* cysts. The inguinal glands were enlarged and hard. Response to emetine injections and quinoxyl retention enemata was immediate.

**Solitary amœbic ulceration of the rectum** —These ulcers, which are palpable on digital examination, may be deep and excavated, with hard craggy margins suggesting by their physical characteristics a malignant growth. Their amœbic nature can be ascertained by scrape preparations made from their surface and they yield most satisfactorily to emetine bisnuth iodide treatment. The author has seen two such cases, both in ex soldiers. In the first amœbiasis was contracted in France in 1917 and urgent symptoms noted 20 years later. The second was contracted in India and had lasted 10 years.

**Fulminating amœbic dysentery** —These cases are rare. Massive destruction of the intestinal mucosa such as occurs in artificially infected kittens may take place in man when the patient succumbs to secondary *Bacillus coli* septicæmia.

Fulminating cases were commonly observed in the Chicago epidemic of 1933. One such case occurred in the author's series (1926). This man had been ill for ten days. On account of the continuous diarrhœa, stupor and associated pyrexia, he had been considered to be an acute case of typhoid. At autopsy numerous multiple amœbic abscesses of the liver were found together with the most extensive ulceration of the whole of the large intestine and massive infection of the blood stream with *Bacillus coli*.

#### COMPLICATIONS AND SEQUELÆ OF AMŒBIC DYSENTERY

**Accidental complications** include perforation of an amœbic ulcer (usually in the region of the cæcum) and consequent general peritonitis. This is nearly always fatal. The author has had experience of four such cases.

**Hæmorrhage** from a perforated artery in the base of an ulcer is another possibility, it also appears to be infrequent and is usually fatal. In the author's experience this accident was encountered three times during the 1914-18 War.

The most common complication is *acute amœbic hepatitis* which is found in about 5 per cent of all cases of intestinal amœbiasis. The onset is sudden, often preceded by a rigor, intense pain over an enlarged liver, pyrexia of a considerable degree, shoulder pain, and other symptoms rather resembling those of liver abscess (see p. 211).

As a sequel of amœbic dysentery various malformations of the colon may be noted. Recent experience has shown that stenosis of the bowel as in bacillary dysentery, does not commonly occur but on the other hand sacculaton of the large intestine with dilatation has been noted. In the author's series two instances of megacolon have been recorded. In both there was a gradual onset of the condition, which took three years to develop after the cure of the amœbic infection.

Stricture of the rectum does not commonly result (see p. 18).

Sprue is a disease which appears to have some connection with amœbiasis. Not only is a double infection of sprue and amœbic dysentery comparatively common but also the former frequently supervenes upon the latter. In 32 per cent of sprue cases it is possible to obtain a past history of intestinal amœbiasis (*see p 338*).

**Cachexia**—There exists an ill defined class of case in which a condition of chronic ill health exists without any outstanding obvious signs or symptoms. These cases are best termed "amœbic cachexia," and increased experience of amœbiasis indicates that they are more frequent than has been formerly suspected. There are records of five such cases in the author's series. In outward appearance, especially the facies, they resemble cases of an early hepatic abscess—the tongue is dirty, the appetite is poor, the complexion is yellowish and muddy, capacity is limited, and fatigue is evident in greater or lesser degree. From physical examination there is little diagnostic guide, but the stools may be found to contain *E histolytica* cysts. Improvement in the general condition of the patient and his appearance after eradication of the infection is striking.

The most pronounced in the author's series occurred in a man of forty-six years of age seen in 1931. The main symptoms were cachexia and extreme fatiguability. He had been an ardent Alpinist but had had to give up all forms of active exercise, and it transpired that he had suffered from amœbic dysentery in Egypt in 1923 and had been incompletely cured with emetine. Various diagnoses had been suggested and surgeons were inclined to regard his condition as intestinal toxæmia due to a chronic appendix. The faeces were found to be heavily infected with *E histolytica* cysts. A remarkable change from his sallow, earthy complexion to that of health took place after a course of anti amœbic treatment.

**Prolapse of the rectum**—Rectal prolapse is brought on by continual straining at stool, it may be the only outstanding sign of the disease, and becomes reduced when the patient is cured of his amœbic infection.

In 1927 the author treated a doctor who had contracted amœbic dysentery in Bagdad in 1922 and who had been treated with emetine injections. Thereafter he suffered almost continuously from rectal irritation and internal hæmorrhoids and, eventually, from rectal prolapse. Examination of the faeces revealed a massive infection with *E histolytica* precystic forms, and cysts. After adequate treatment the prolapse receded and the piles disappeared. He has since been in good health.

**Pericolic abscess**—Obstruction of the large intestine, complete or partial, may be brought about by the formation of a pericolic abscess. In this state amœbic ulceration proceeds towards the peritoneum and causes perforation with formation of a localized abscess.

In the Hospital for Tropical Diseases, London, one case occurred of undoubted amœbic origin, which was successfully operated upon by Mr C N Morgan and I am indebted to my colleague Dr Carmichael Low, for his permission to refer to this case. The patient was admitted in 1930 with a

history of amœbic dysentery of two years' duration. *E. histolytica* in the active state were present in the faeces and were also demonstrated in scrapings from the rectum. After treatment with emetine bismuthous iodide, he recovered. Four years afterwards he was re-admitted with a palpable tumour in the left iliac fossa, which varied in size from day to day. Barium enema showed a long filling defect ( $3\frac{1}{2}$  to 4 in.) situated in the descending colon immediately distal to the splenic flexure. At operation a large inflammatory mass (pericolic abscess) was found involving the splenic angle and descending colon and extending backwards to the vertebral column. Removal of the mass was unjustifiable and in fact, impossible, and a lateral anastomosis was performed between the transverse and sigmoid colons. Recovery was uneventful. (Plate VIII, p. 155.)

**Hæmorrhoids.**—External piles are a very frequent accompaniment of intestinal amœbiasis. Almost every case of long standing shows evidences of them, and they are also associated with prolapsed internal hæmorrhoids, produced by continuous straining at stool, so that they disappear when the underlying cause has been removed. The hæmorrhage from the piles when appearing in the faeces must be distinguished from the exudate of the amœbic ulcers. It is usually of a darker, somewhat purple colour.

**Spasticity of the sigmoid colon.**—Spasm of the large bowel occurs in amœbic dysentery, especially in longstanding cases, and in those in which periodical constipation is a feature. Spasmodic contraction may predominate over other symptoms and be ascertainable by abdominal palpation.

**Amœbic ulceration of the appendix.**—Amœbic disease of the appendix is by no means common, though chronic inflammatory appendicitis as a sequel to intestinal amœbiasis is not unusual. In the author's series of seventy three cases of appendicitis from the tropics coming to operation, fifteen had a definite previous history of intestinal amœbiasis, nineteen of bacillary dysentery, two of sprue. W. E. Musgrave (1910) reported three deaths from perforative ulceration of the appendix in intestinal amœbiasis. Usually the causative organism is a streptococcus, or *B. coli*, which may be associated with amœbic invasion of the bowel.

F. P. Hogan (1920) gave a detailed description of such a case studied both from the clinical and pathological aspects; amœbæ were demonstrated *in situ* in the tissues of the appendix. A. V. Greaves (1933) has added yet another well authenticated case, that of a Chinese girl aged five years, in Hong Kong. Generalized peritonitis was present and the appendix was found to be ruptured and adherent. The ulcerated area consisted of three separated ulcers leading into a large undermined necrotic mass in sections of which numerous entamœbæ were demonstrated on microscopic section.

H. C. Clark (1924), in a review of routine post mortems in Panama, found seventy six cases of amœbic ulcerative appendicitis resulting in 9.2 per cent., in perforations or abscess formation. In half of the autopsy cases in which amœbic ulceration of the colon was found the appendix was also involved.

**Neurasthenia.**—C F Craig (1929) has made a study of "latent" amœbic infection, the symptoms of which are confined chiefly to the digestive and nervous systems, and he describes certain definite neurasthenic manifestations. That the form found commonly in the tropics or "tropical neurasthenia" is frequently associated with chronic amœbiasis, nobody with a prolonged clinical experience can deny.

**Other sequelæ.**—Chronic diseases of the intestinal tract which seem especially apt to follow in the wake of intestinal amœbiasis are mucous colitis (*see p 421*), duodenal ulcer, and appendicitis. By this the author means, not that these intestinal sequelæ tend to arise at some considerable period after successful treatment for amœbiasis, but that they may legitimately be regarded as legacies of amœbic infection. He has been under this impression for many years, and on a reference to the records at the Hospital for Tropical Diseases the following figures emerge—

In the author's series of forty cases of duodenal ulceration as proved by X ray examination, fourteen gave a previous history of amœbic and six of bacillary dysentery. In eight consecutive cases diagnosed by barium meal as duodenitis, only one had a previous history of amœbic and three had a history of bacillary dysentery.

On the other hand, there are singularly few records of gastric ulcer in old dysenteric patients. Out of twelve proven cases two had had intestinal amœbiasis and three bacillary dysentery.

There were twelve records of post dysenteric dyspepsia of which six occurred subsequent to amœbic dysentery—one of them had achylia gastrica the other hypochlorhydria.

In seventeen cases of diverticulitis which were investigated no association with previous amœbiasis was forthcoming.

**Carcinoma.**—J G Willmore\* has shown that carcinomatous changes may take place in longstanding amœbic ulcers and he has traced the history of nine instances of malignant disease of the colon developing in amœbic patients. In one he observed an amœbic ulcer, and was able to recover *E. histolytica* in scrapings, but on re-examination six weeks after, a malignant growth was found at the same situation.

The author has also encountered two cases of carcinoma of the rectum in association with subacute intestinal amœbiasis. It has been a common experience to find a carcinoma of the rectum or sigmoid colon in elderly patients suspected of dysentery.

A C Reed and H H Anderson (1936) investigated four cases of chronic amœbiasis in which carcinoma of the colon followed and accompanied the amœbic infection. They concluded that amœbic lesions may produce carcinomatous changes in two ways—by chronic irritation and by the production of benign adenomata which later become malignant. In three the new growth was situated in the sigmoid and in one in the cæcum.

\* Personal communication.

*Cicatrizaton and stricture of the colon or rectum.*—Contrary to assertions, stricture of the bowel due to amœbic ulceration is extremely rare. One case with pericolicitis, which was relieved by colostomy, has already been referred to (p. 166), but this is the only authentic instance which has come under the author's notice, while Sir L. Rogers, who has examined over five thousand specimens in the Calcutta Museum, has recorded that he has never seen a genuine stricture.

## CHAPTER XII

### AMŒBIASIS (*continued*): DIAGNOSIS OF AMŒBIC DYSENTERY

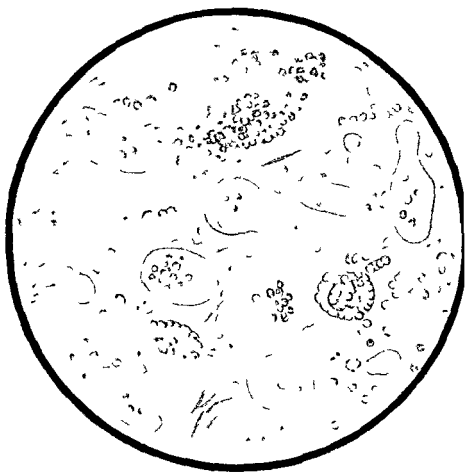
**Microscopic examination of fæces**—To render the diagnosis of intestinal amœbiasis absolutely certain, it is necessary to demonstrate the *Entamoeba histolytica* free or encysted. It must not be thought, however, that a single microscopical examination will suffice, so varied and almost bewildering are the morphological phases of this parasite, that the examination should be performed by one who has long made himself familiar with it. For not only have the varying appearances of the amœba to be considered, but also its differentiation from other parasitic protozoa which may inhabit the human intestine and from inflammatory and body cells derived from the intestinal canal (Fig 22). The cysts of *E. histolytica* may be easily confused with vegetable organisms, cells, and even with food. Experience and accuracy in diagnosis can be acquired only by constant practice, and in the author's opinion this takes months, if not years, of study (Plate IX).

In the acute stage of amœbic dysentery, when blood and mucus are passed in the stools, the active and dividing forms of *E. histolytica* are present. The cysts, which are more difficult to diagnose with certainty, are found in the faecal contents during the chronic stage, and are never encountered in a blood and mucus stool.

Moreover, the various stages of *E. histolytica* found in the stools may afford valuable diagnostic data. For instance, the carrier of *E. histolytica* passes normal stools containing cysts but no active amœbæ. If purged, he probably passes amœbæ very rarely large, tissue invading forms containing red blood corpuscles. In the acute stage, however, nearly all amœbæ are of the tissue invading type. In liver abscess, the amœbæ in the pus are tissue-invading forms, cysts or precystic amœbæ are never produced. On the other hand, it is exceptional to find tissue-invading forms in chronic amœbic dysentery.

Difficulties connected with the microscopic diagnosis of amœbic dysentery must be emphasized. The portion of the stool most likely to reveal organisms is one which contains mucus streaked with blood, for in these blood clots amœbæ, singly or in aggregations, may most readily be demonstrated. They are not always uniformly distributed throughout the exudate but in colonies, so that failure to find them in one or two microscopic fields is not necessarily conclusive. Sometimes it is possible to demonstrate amœbæ in scrapings from the bowel





*P. H. Manson Bahr del*

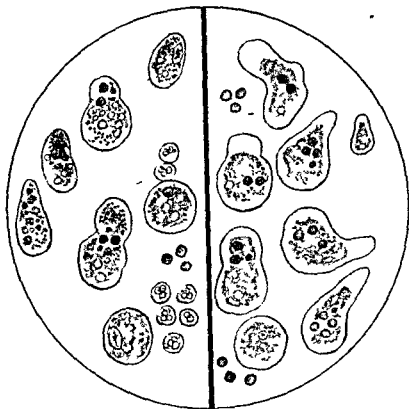
### MICROSCOPIC APPEARANCE OF EXUDATE IN AMÆBIC DYSENTERY

Fresh preparation Shows active *Entamoeba histolytica* Some with ingested red blood-corpuscles, acicular Charcot-Leyden crystals and disintegrated intestinal epithelium

PLATE IX

surface when examination has proved negative. In those patients with secondary amœbiasis, such as liver abscess, the fæces may contain no evidence of amœbic infection.

In the chronic stage it is often difficult to find cysts. For some reason, they may appear in large numbers once, then disappear even when conditions appear favourable, it is, therefore, necessary to



P. H. M.-B.

Fig. 22.—Diagram showing differentiation of *E. histolytica* from tissue cells.

Left: macrophage cells and pus cells in exudate of bacillary dysentery with ingested red blood-corpuscles. Right: *Entamoeba histolytica*, active and precystic forms in amœbic dysentery stool.

examine specimens on six or more consecutive days before establishing a negative diagnosis. Under these circumstances it is more likely that amœbæ and cysts will be found if the patient is freely purged with a saline. Castor oil and only medicaments must be avoided, for the drop lets so produced render it impossible to examine the stools with any degree of accuracy. E. Reichenow (1926), however, who made daily observations on his own excreta for six months, found, by counting the cysts that they diminished in numbers after a saline purge. P. Ravaut

and G. Krolunski (1916) advocated intravenous injection of 1-4 cgm of mercuric cyanide which, they state, increases their numbers.

It is hardly necessary to emphasize that, for successful microscopic diagnosis, the faeces must be fresh, especially in the acute stages, for amœbæ degenerate and die rapidly outside the body, usually within two hours. The cysts, on the other hand, being designed by nature for external life outside the body, remain alive and recognizable in the stools for days—even for several weeks—under ordinary conditions. If a few drops of formalin be added, the cysts in the faeces will retain characteristics almost indefinitely.

Where cysts are scanty, repeated examinations increase the chances of detection, thus D. L. MacLennan recorded that after six examinations the percentage of positive findings is increased eightfold. In 1,680 faeces examined on one occasion only the percentage of positive findings was 4.8, but after six examinations it increased to 84.6.

W. M. James (1927), working with fresh material, and with permanent preparations, has been led to believe that in trained hands positive results can be expected at the first examination in 75 per cent. of cases, but at a second the percentage is increased to 90. Should a third examination not disclose a *histolytica* infection, positive results need not be expected.

At the Hospital for Tropical Diseases, London, the three stool examination test is adopted as a routine. It has proved to be the most convenient and economical method, although an occasional case may thereby be overlooked. In the author's series of 535 proven cases of intestinal amœbiasis (1941) active *E. histolytica* were found in the faeces in 222, *E. histolytica* cysts and precystic forms in 287, and *E. histolytica* in scrapings from rectal ulcers, but not in faeces, in 26.

**Technique of microscopical examination**—This subject is fully dealt with in the Appendix (p. 551). It is only necessary to emphasize that the stools should be as fresh as possible, and when they contain blood and mucus a portion of this should be selected for microscopical examination. A warm stage is not necessary if the stools are freshly passed and are kept at body temperature in a warm room. As N. D. Fraser (1927) has pointed out, the amœbæ and cysts can be recognized primarily under a low power ( $\frac{1}{2}$  in objective) as 'bright stars,' being of higher refractivity than surrounding cells. (Fig. 23.)

Methods of concentrating amœbic cysts to facilitate their detection have been elaborated by many. J. W. Cropper and R. W. H. Row (1917) used a saline and ether concentration, but the technique of C. F. Craig is the one recommended. (See Appendix p. 555.)

J. G. Thomson and A. Robertson (1921) who paid attention to the presence of Charcot-Leyden crystals in amœbic dysentery stools, found them in 25 per cent. of proven cases of intestinal amœbiasis. They are most common in longstanding infections with *E. histolytica*; their number varies greatly and does not appear to bear any relation to the severity of the disease. Crystals are numerous at the site of amœbic ulcers, and it is thought that they may

result from cytolysis of eosinophil cells or may be an excretory product of the amœba

We may conclude that Charcot Leyden crystals are not necessarily diagnostic of amœbic dysentery, but may constitute a useful indication

**The sigmoidoscope as an aid to diagnosis**—Lesions of amœbic dysentery occur in the rectum and the sigmoid in over 80 per cent of the cases of this disease and extend down to the internal sphincter. As seen in the living subject, these lesions are quite distinctive, but differ considerably in appearance from the grosser lesions seen in pathological specimens. After death, the more superficial and dis-



P H M B

Fig. 23 —Chronic amœbic dysentery feces preparation showing two cysts of *Entamoeba histolytica* and one of *Entamoeba coli* (unstained)

tinctive details disappear and many of the delicate tints which characterize the living ulcers are lost. Moreover some lesions are so small that they can be distinguished only by means of a magnifying lens and therefore become unrecognizable post mortem. The clinician who undertakes sigmoidoscopy for intestinal amœbiasis must provide himself with a microscopic eyepiece with a lens magnifying two or more diameters. It is not possible to diagnose every case of intestinal amœbiasis by means of the sigmoidoscope, because in a certain proportion lesions are confined to the cæcum and ascending colon, far beyond visible range.

Not only can the character of amœbic lesions be recognized by sigmoidoscopy, but amœbæ may be demonstrated in scrapings taken

from lesions by a special spoon (see p 10) The edge must not be so sharp as to destroy the lesions and cause hæmorrhage, nor yet too blunt to remove sufficient tissue for examination Difficulty may be experienced in transferring the small amount of material from the hollow of the spoon, a porcupine quill forms the best instrument for this purpose The material thus obtained is suspended in saline, covered with a slip, and examined without delay Sometimes it is difficult to obtain sufficient material in the hollow of the spoon, and it is then better to scrape the exudate into the sigmoidoscope The author's statistics are based upon 535 cases of amœbic dysentery definitely diagnosed in the years 1920-39 Of these, 509 were diagnosed by microscopical examination of the faeces, sigmoidoscopic examinations were made in 258 and lesions demonstrated in 234 In 77 *E histolytica* was found in scrapings, in 24 (9·8 per cent) the mucosa appeared normal The author has also shown that cysts of *E histolytica* are usually more numerous, and therefore more easily detected, in the faeces which are adherent to the mucosa and removed through the sigmoidoscope

*Acute stage*—The distinctive characteristics of amœbic lesions, as compared with those of bacillary infection are their superficiality, the comparative painlessness with which the examination can be carried out, and the laxity and elasticity of the mucous membrane The ulcers are scattered so that the intervening mucous membrane remains normal Individual ulcers are small—only a few millimetres in diameter—and never, in the author's experience, resemble the large, undermined, oval shaped ulcers so often encountered post mortem In addition to ulceration small hæmorrhages are frequently seen, surrounding the ulcers or scattered haphazard These are petechial in the submucosa but larger ones are often observed in niches between the folds of mucous membrane (Plate V, E, facing p 78)

The earliest amœbic lesions in the rectum consist of small yellow elevations with a hyperæmic margin, which mark the site of future ulcers In association with these elevations, fully developed amœbic ulcers can usually be distinguished In the acute stage, necrosis of the mucous membrane may progress to a considerable degree The lesions at first isolated and disconnected, may coalesce, producing a ragged granulating and bleeding surface which may closely resemble granular stages of bacillary dysentery, or ulcerative colitis It should be noted that the normal folding of the mucous membrane is exaggerated in amœbiasis When scrapings are made from the hæmorrhagic surface, amœbæ may sometimes be demonstrated This surface infection resembles the intense condition produced in experimental amœbiasis in kittens These lesions usually extend down the rectum to the internal sphincter and occasionally to the anal margin

In America W C Boeck and W D Smith, G S Gant and L A Buie have devoted attention to amœbic lesions as seen by the sigmoido-

scope They point out that the amœbic ulcer occupies a position on the prominent folds of the bowel wall, or usually involves the valves of Houston The margins are undermined by infiltration of the ulcerative process, and the prominence of the ulcer is further increased by the accumulation of inflammatory tissue at the base, so that it projects above the ulcer margin and presents itself as a greyish white covering, known as the "white cap," over the centre of the ulcer. This white cap is swabbed away, and the true base of the ulcer is revealed, lying below the surface of the overhanging margins

Although it is possible for a trained proctologist to recognize amœbic colitis by the characteristic ulcers, yet certain diagnosis is best obtained by demonstrating the amœbæ, in order to do so Buie has devised a method of removing a small piece of tissue from the overhanging margin of the ulcer wall and examining it directly under the microscope The material collected by biopsy is transferred to a glass slide and covered with a few drops of physiological saline solution, but in the author's experience this method usually produces too much bleeding to be of any practical value

*Subacute stage*—Here the bowel presents the same rugged folded appearance, but much blood stained mucus is usually present in the lumen Amœbic lesions may take the form of the minute yellow papules which have already been described, and various stages may be observed between them and the typically developed ulcer Very often small depressions of the mucous membrane with hæmorrhagic bases can also be distinguished, they may be so minute as to require a magnifying eyepiece for their recognition, but it is not usually possible to find amœbæ in scrapings from these lesions (See Fig 13, p 77)

*Chronic stage*—This is the stage in which it is most difficult to make a definite diagnosis, and laboratory methods so often fail Sometimes the culture method from the bowel scrapings succeeds where a fæcal microscopic examination does not Usually small superficial pits of the mucosa may be present, or definite deep ulcerations may be visible, with undermined edges, hæmorrhagic margins, and yellowish or grey coloured bases (Plate V, D, facing p 78)

*Solitary rectal amœbic ulcer*—On rare occasions a large ulcer, 1-2 cm in diameter, is seen inside the anal margin, and may give rise to considerable pain and bleeding The author has encountered cases which were suspected of being malignant in origin, but which on scraping proved to be due to the *E histolytica* It is important, therefore, that any ulcer of the bowel in a patient coming from an endemic zone of the disease, should be examined from this viewpoint (Plate V, C, facing p 78)

A case of indurated ulcer of the rectum, which on digital examination gave the impression of malignancy, occurred in the author's practice *E histolytica* were demonstrated in scrapings from an ulcer 9 cm from the anus, and other lesions were subsequently found at a higher level in the rectum and sigmoid The patient had, apparently, been originally infected

in France in 1917, and it had taken twenty years for symptoms of rectal bleeding to develop. This large indurated ulcer granulated up within seven days from the commencement of emetine bismuth iodide treatment and three weeks later had epithelialized, within a month no traces of the former ulcer could be seen. A second case—an Indian infection of ten years' duration—was subsequently recognized.

*Latent amœbic dysentery*—Of all bowel diseases intestinal amœbiasis is most remarkable for its periods of latency. The patient may, after an initial attack, remain free from all external signs and symptoms of the disease for a period as long as five six, or even seven years. It is therefore important that some distinctive appearances of the bowel surface should be recognizable. Lesions in these latent cases often take the form of small yellow papules, or the whole surface of the rectum may be studded with microscopic depressions or pits (a pock marked appearance) which represent healed ulcerations but may be difficult to detect.

*Carrier state*—Interest especially centres in lesions which can be seen in those who are carriers or 'cyst passers' of the amœbæ, that is to say, persons who although showing no symptoms or signs of dysentery yet continue to pass cysts of *E. histolytica* in their faeces. By sigmoidoscopy the bowel usually appears normal but sometimes granular patches or small scattered hæmorrhages alone indicate the site of minute amœbic ulcers.

*The sigmoidoscope as a guide to treatment*.—The lesions in various phases of amœbic infection can be observed to change considerably during treatment. The author has studied them during the course of treatment with emetine bismuth iodide and quinoxy. Healing is remarkably rapid. Within twelve days from the commencement of the treatment epithelialization has already taken place and in a short time it becomes difficult to recognize the site of the former ulcers. In a healed bowel active signs of amœbic infection are absent though small depressions or pits stud the mucosa and remain visible for years.

*The blood count as an aid to diagnosis*—In acute cases of intestinal amœbiasis the average red cell count varies between four and five million per cubic millimetre while the average hæmoglobin content is between 65 and 75 per cent. There is usually a moderate leucocytosis, averaging about 10,000 per cmm. Cases showing a higher count should arouse suspicions of a possible liver abscess. The author, with H. M. Willoughby (1928), from an analysis of 165 proven cases of intestinal amœbiasis showed that in acute cases with diarrhoeic or dysenteric symptoms an average leucocytosis of 11,000 with a relative reduction of the polymorphonuclear leucocytes to 64 per cent was present. In chronic cases however there is no leucocytosis, but a relative decrease of the polymorphonuclears to 57 per cent and a slight increase of the lymphocytes to 34 per cent. As a working rule, the leucocyte count is higher in intestinal amœbiasis than in bacillary dysentery.

**Complement-fixation and other serological tests**—C F Craig, in his most recent publications stresses the value of this test in diagnosis, though at present, on account of difficulties in preparation of the antigen it is of academic value only. The technique employed is practically the same as that used for the Wassermann reaction (the standard method for the complement deviation test for syphilis). Craig has now published the results obtained in 1 000 cases, in which the findings were checked by an examination of the faeces for *E histolytica*, 17.5 per cent gave a positive result and 82.5 per cent a negative one. Of the 175 persons giving a positive reaction, *E histolytica* was found in the faeces of 157, or 89.7 per cent. On the other hand *E histolytica* was found in the faeces of 1.4 per cent of the 825 who gave a negative complement fixation test. It is claimed that the test possesses a degree of specificity and becomes negative after treatment. T B Magath and H E Meleney (1940) compared the results of tests from two independent laboratories: a positive result was returned in 32 per cent, and reports failed to agree in 16.7 per cent. It is evident that considerable improvement in the preparation of antigen is necessary before this test can be relied upon.

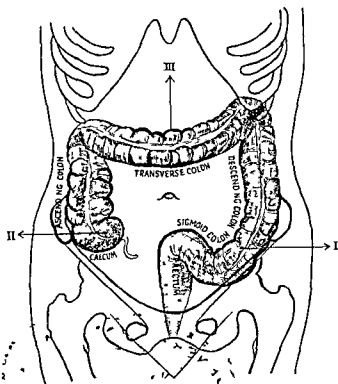
In studying precipitins in cats infected with *E histolytica* E H Wagener in 1924 prepared test antigens by placing scrapings of ulcerated bowels from infected cats in Coers's extracting fluid for several days, and subsequently filtering. The test was performed with twenty-five infected and five normal cats. Fairly satisfactory precipitin tests were obtained.

**Intradermal tests**—As aids to diagnosis attempts have been made to elaborate an intradermal test, such as that of L Scalas (1923). The test material was prepared by mixing 80 grammes of mucus and fragments of the intestinal mucosa obtained from an acute case of amoebic dysentery with 80 c.c. of physiological saline solution incubating for a week at 37° C with daily shakings and filterings and finally decolorizing with animal charcoal. In positive reactions the injection of 0.25 c.c. intradermally was followed in an hour by swelling and redness accompanied by itching and a sense of heat. These signs disappeared in one to three days. As the results were somewhat indefinite, it is essential that these experiments should be repeated, using a test material containing a higher concentration of amoebic substance, possibly from cultures.

**X-ray appearances as an aid to diagnosis**—The author has found X-ray examination of the large intestine by the barium enema method to be distinctly disappointing as an aid in the diagnosis of amoebic ulceration of the bowel, especially where extensive ulceration of the rectum can be seen by sigmoidoscopy, and where clinically, the caecum is involved. Occasionally, filling defects have been observed in this viscus, but similar appearances are seen in forms of dysentery and colitis unconnected with *E histolytica*.



J J Vallarino stressed the filling defects in the caecum and other minor appearances observed in the outline of the large intestine. H M Weber has drawn attention to the abnormally small and often irregular caecum observed in all cases of definitely diagnosed chronic amoebic



P H M B

Fig 24—Diagram illustrating diagnostic points in the clinical diagnosis of amoebic dysentery

The arrows mark the position of deep tenderness on palpation. I amoebic focal point on pressure of the first portion of the sigmoid against the pelvic brim. This is present also, sometimes, in chronic ulcerative colitis, and in chronic bacillary dysentery. II may be found alone or in association with I. III giving rise to epigastric tenderness, may cause confusion with gastric or biliary disease. The heavily-outlined portions indicate the areas of amoebic infiltration which can be elicited on deep palpation. Grosser degrees of infiltration are found at I and II in diverticulitis, and at II in Crohn's disease, in intestinal bilharziasis and also in tuberculosis of the caecum.

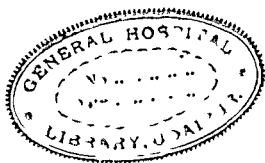
dysentery and also the marked incompetence of the ileo caecal valve, which permits unobstructed flow of the opaque material from the caecum into the terminal ileum. K Ikeda has described the same deformity, together with changes in the valve in cases resulting from the Chicago epidemic of 1933. In acute cases of amoebic dysentery J C Bell (1936) has confirmed these findings and describes a peculiar

and striking 'cone like' deformity of the ileo caecal valve, as well as a deformity of the lower end of the caecum

G Mather Cordner\* reports on radiographs of more than 150 cases of proven amœbiasis by the opaque enema. In only two has he observed deformity of the caecum with incompetence of the ileo caecal valve comparable to that described by J C Bell. In one case this deformity was proved to be inconstant. In non amœbic cases six were similar. In his opinion it is possible to assume the existence of colitis, but not the specific nature of the lesion.

**Differential diagnosis** of intestinal amœbiasis from diverticulitis, ulcerative colitis, bacillary dysentery, mucous colitis, intestinal bilharziasis, polyposis, and other forms of intestinal disease is fully dealt with in the sections which treat of these conditions (Fig 24)

\* Private communication



## CHAPTER XIII

### AMŒBIASIS (*continued*) : THE TREATMENT OF AMŒBIC DYSENTERY

THE treatment of intestinal amœbiasis is a problem to which much attention has been paid, and developments in this direction have been extensive. It may justly be claimed that, at the present day, medical science has more complete control of *E. histolytica* and its effects than of any other human parasitic infection.

The treatment of intestinal amœbiasis is directed towards extirpation of the parasite, and, at the same time, the clinical cure of its host by restoration of damaged tissues.

If it is permissible to crystallize the results of experience in an epigrammatic statement, it may be said that the more acute the attack of amœbiasis and the more striking the symptoms, the more dramatic the cure and the more permanent the results.

**Ipecacuanha.**—Ipecacuanha is the powdered root of a rubiaceous plant *Cephaelis pychotria* (or *Urugoya ipecacuanhæ*). In acute intestinal amœbiasis the older generation of physicians obtained really remarkable cures by its use. E. Parkes appears to have been the first—as early as 1846—to exhibit the full doses of 30–60 grains. In 1896 Norman Chevers and N. C. Maclean advocated it as preventive treatment in liver abscess, but their observations were largely forgotten in subsequent decades.

The ipecacuanha root contains at least four alkaloids, of which the most important are emetine, cephaelin, psychotrin, and methyl psychotrin. The two toxic substances are emetine and cephaelin, which may cause gastro-intestinal symptoms, nausea, vomiting, and diarrhœa, but which are specific for *E. histolytica*.

**Emetine.** *History.*—Emetine was isolated from ipecacuanha by Pelletier as early as 1817, and attempts were made to treat dysentery by its aid, but it was discarded on account of its emetic properties.

In 1911 its lethal action was first established by E. B. Vedder, and its power of destroying amœbæ with startling rapidity was pointed out by Sir L. Rogers. Although his observations were doubted at the time, they have since been abundantly confirmed by C. A. Kofoid and E. H. Wagener, working with cultures of amœbæ, and, more recently, in a dilution of one in a million, by C. Dobell and by J. H. StJohn. The last observer found that the drug acts best in an alkaline medium.

Various derivations of emetine, such as dimethyl emetine, n methyl emetine, and iso emetine (Pyman) also have an action upon *E. histolytica*. Clinical evidence points to the fact that amœbæ acquire a tolerance of

emetine after being subjected to its action. Thus A. Halawani (1930) has demonstrated an increased resistance by amœbæ in culture.

**Dosage**—Emetine remains the sheet anchor in acute cases of intestinal amœbiasis. It is considered that the optimum dose is 8–12 grains for an adult and it is generally conceded that a continuous dosage of over 15 grains may be followed by toxic manifestations. Emetine in tablet form by the mouth has proved useless as it provokes emesis.

**Method of administration**—There has been much discussion on the method of injecting emetine. It is apt to cause eczematous patches if given subcutaneously, and when injections are repeated in too limited an area and in those who have an idiosyncrasy abscess formation or even extensive ulceration of the skin may appear at the site of the injection. Deep subcutaneous injections i.e. into the subcutaneous tissue are much better tolerated and much less painful. When emetine is injected into the muscular tissues every care must be taken to eliminate any source of focal sepsis first or a fixation abscess may occur at the site of the injection. The author had an alarming experience of this, when in one of his recent cases a large gluteal staphylococcal abscess formed at the site of injection a metastasis from a septic prostatic abscess.

Intravenous injection does not find many advocates at the present time. The drug is much too toxic and is especially likely to act upon the heart.

It is generally agreed that emetine is the most useful drug in the early stages of hepatic amœbiasis, in this condition subcutaneous and intramuscular injections are followed by the best results.

Owing to its possible toxic action this drug should not be exhibited while the patient is leading an active life. It is a depressant both physically and mentally, so that if a patient cannot be kept in bed at least he should not be permitted to undertake active physical exercise.

The action of emetine on *E. histolytica* in the stools is very rapid.

In 1932 the author, on sigmoidoscopic examination of a case of amœbic dysentery found numerous active ulcers containing amœbæ. Four days later after the exhibition of 3 grains of emetine the bowel was re-examined and it was found that the ulcers had already commenced to heal and the amœbæ had disappeared.

The action of emetine has been studied by W. M. James (1913). He discovered that changes in the cytoplasm of the amœbæ in the faeces occur after an initial dose of one-sixth of a grain of emetine. After 4 grains the nucleus becomes disintegrated.

L. Rogers considered that for a full grown man over 12 stone (76.2 kilo) a dose of 1½–2 grains should be given daily for the first three days and subsequently one grain daily should be continued. To children of eight years of age half a grain should be administered and to still younger ones one sixth. (According to A. C. Reed the

total amount of emetine in one course should not exceed 0.01 grammes per kilo body weight )

In addition to emetine injections Rogers originally advocated the administration of  $\frac{1}{2}$  to 1 grain doses of emetine by the mouth presumably given in keratin coated capsules, or the combination of emetine injections with powdered ipecacuanha 20-30 grains. The object of this mass attack is to destroy *E. histolytica* while still in the active and vulnerable stage.

*Emetine by enema* —Attempts have been made by the author to introduce emetine directly into the bowel. This causes a considerable amount of pain and is by no means successful. Even when given in a dilution of 1 : 1000 (4 grains in 10 ounces of normal saline) violent spasms were produced and parasitic relapse with blood and mucus in the stools ensued.

*Results* —Experience has shown that, though the immediate therapeutic effects of emetine are most striking, this drug alone does not succeed in eradicating the infection *in toto*. It is efficacious solely in the acute stage of the disease with active entamoebae, but has no effect whatever in the chronic form when cysts are present.

In eighty seven cases investigated by the author in London, 1920-2, more than half (forty eight) had sustained a relapse. These patients contracted their infection during war service and gave a subsequent history of relapses over a period of four to six years. All had received prolonged treatment with emetine injections, two having been given as much as 70 grains consecutively, and one as much as 120 grains, the average in most cases being 8-16 grains.

The *toxic effects* of emetine are important. They consist of asthenia, weakness, cardiac irregularity, fall in blood pressure, mental depression, desquamation of the skin, brittleness of the nails, myositis, neuritis, and diarrhoea. This diarrhoea is of special note in that it is not generally recognized and may lead to continued emetine therapy in the belief that it is due to the disease. Nearly every patient undergoing emetine therapy complains of mental depression, weakness, and loss of sense of taste for food and tobacco, a fall of blood pressure of 10 mm. or more of mercury can usually be registered. In extreme cases paresis of the legs, with toe or foot drop, loss of knee jerks and some degree of paresthesia have been encountered.

Occasionally emetine may attack one particular group of muscles, producing a condition resembling early progressive muscular atrophy. This is probably a true myositis, since the atrophy is preceded by myotatic irritability and muscular pains.

In June 1920 the author was consulted by a doctor who was very sensitive to emetine. He had suffered for four years from recurrent attacks of amoebic dysentery for which he took emetine injections, on each occasion he noted that the muscles of the left shoulder girdle became affected after 12 grains had been injected. Finally, he took a course of 27 grains of emetine bismuth iodide which caused vomiting and diarrhoea. A condition resembling early progressive muscular atrophy was then noted affecting the trapezius, the supra and infra spinatus and to a lesser degree the deltoid. Finally after

three months' treatment with massage and electricity, muscular function was once more fully restored

W A Young and G R Tudhope (1926), from their experimental work, consider that the action of emetine is concentrated upon the muscle fibres rather than upon nerve endings

The effect of emetine upon the cardiac muscle is a subject which has attracted the attention of pharmacologists, and to which too little attention has been paid by the practitioner in the tropics R N Chopra and B Sen found that the systolic blood pressure falls to 90 and 100 mm after emetine therapy, and tachycardia of sinus origin—even auricular fibrillation—results Lethal and sublethal doses cause severe injury to the myocardium in rabbits, but some time elapses before the morphological changes become apparent, when given in large doses the heart beats are slowed, weakened and fade away Auricular fibrillation may precede heart failure while with increasing doses respiratory paralysis may be produced

When giving emetine in pregnancy and after parturition it should be remembered that it has an effect upon the uterus, as has been demonstrated by D Epstein in cats

In minor degrees of emetine intoxication the patient complains of weakness of the calf muscles often associated with numbness and paræsthesia of the soles Very commonly after a course of emetine bismuth iodide stiffness persists in the legs for a considerable period

The author has notes of four cases of emetine intoxication in which the effects were so severe as to give rise to some anxiety The first case had received a total of 59 grains of emetine by injection which had been given him consecutively for amoebic dysentery contracted in Nigeria He had advanced neuritis of both legs and hyperæsthesia of the calf and thigh muscles Recovery was eventually established after three months treatment In the other cases extreme weakness of the muscles was the cardinal feature with loss of reflexes In one man of fifty three who had received 16 grams of emetine bismuth iodide both arms and legs were affected In 1929 the author saw a man of forty four who had paresis of both legs with loss of deep reflexes atrophic skin and brittleness of nails following upon emetine injections which had been given continuously over a period of two months

Although emetine is the most efficacious drug in the acute stage, yet the author contends that only rarely does it entirely eliminate the infection, so that an after course of emetine bismuth iodide is necessary

The widely practised procedure of periodic injection of emetine is in the author's experience, to be deprecated, as it merely tends to render *E histolytica* emetine resistant These clinical observations receive support from the laboratory experiments of H Bonnin and R Aretas (1939) who, by exposing *E histolytica* in cultures to increasing concentrations of emetine, found it was possible to produce strains resistant to this drug

*Emetine bismuthous iodide* (*Emetine et bismuthi iodidum*, B P, 1932) (T B I)—The combined iodide of emetine and bismuth is prepared

by precipitation from a solution of emetine hydrochloride by the addition of a solution of potassium bismuth iodide. It contains not less than 25 per cent and not more than 28 per cent of emetine ( $C_{10}H_{14}O_4N_2$ ) and not more than 18 per cent of bismuth.

This drug was introduced for the treatment of chronic intestinal amœbiasis by A. G. Dumez in 1915, and its effects were first tested on man by H. H. Dale, and by G. C. Low and C. Dobell in the following year\*. It soon became apparent that it was more efficacious in eradicating cysts and in curing chronic cases than was emetine. Since that time a great deal of work has been carried out with this drug.

Emetine bismuth iodide is a brick red powder which is usually dispensed in hard gelatinous capsules known as 'shipules' (Martindale), each containing one, two or three grains of the drug. If the full dose of 3 grains is to be given, it is better from the point of view of the patient to administer it in one capsule. The drug is also dispensed as a hard tablet or mixed with excipients such as vaseline, stearin, soap, or resin. It is sometimes put up in pills coated with keratin but experience has frequently shown that they are apt to be passed unabsorbed in the stools. Probably salol coated pills are more readily absorbed (D. G. Lillie and S. Shephard).

In treating patients with E. B. I., it is necessary, to give the drug full effect, that the patient should be confined strictly to bed. In subacute and acute cases this is usually not difficult, but patients who are chronic carriers without definite symptoms may object. Unless rest is enforced, however, vomiting will almost certainly occur, and there may be diarrhœa, which almost invariably follows E. B. I., and the danger of heart trouble.

The rationale in E. B. I. lies in the fact that emetine is liberated on the surface of the bowel. The bismuth salt is converted into the sulphide after passing the pylorus. The reaction is slow, taking place as the compound is spread over the surface of the intestines.

Intensive E. B. I. treatment may be trying to the patient, for it is an irritating drug. When first introduced it was considered necessary to keep the patient strictly to bed for three weeks on a milk dietary, but this did not appear satisfactory as it resulted in considerable loss of weight (5-10 lb) and a fall of blood pressure, an average of 20 mm (systolic). Subsequent experience has shown that it is not necessary to diet the patient so strictly. (See the diet sheet, p. 189.)

The best method is to give a preliminary aperient consisting of oilum ricini, half ounce and tinctura opii 15 minims and to commence treatment with small doses such as 1 grain, working up to the maximum of 3 grains given last thing at night. Formerly it was considered that 30-36 grains of E. B. I. given consecutively were necessary to eradicate infection, but it now appears that much smaller doses

\* It appears that a case of dysentery was treated by Tull Walsh in India with the double iodide of emetine and mercury as long ago as 1891, with preparations which were advocated by Warden.

(e.g., 19 or 20 grains) are just as efficacious. Results are equally satisfactory when individual doses do not exceed 2 grains.

In order to avoid nausea or vomiting E B I should be given on an empty stomach and last thing at night, when the patient is in bed and resting. No solid food should be administered for three hours before the drug. It may then be taken with a small quantity of tea or water, a sedative, *tinct. opii*, 10 m, chlorotone 10 gr, or luminal, 1 gr, should be administered half an hour previously. The pillows should be removed, and the patient should be laid flat on his back and warned to remain perfectly quiet. Any saliva which has accumulated in the mouth should be expectorated. Vomiting may occur immediately after the capsule has been administered, the contents being returned as red powder. "Therapeutic vomiting" may occur two to four hours subsequently, and this is due to release of emetine in the small intestine. If vomiting should become excessive, a turpentine stupe or mustard leaf should be applied to the epigastrium. Bradycardia associated with nausea and low blood pressure may be taken as an indication of intolerance to further E B I.

Successful E B I treatment is followed by a diarrhoea in which the stools assume a dark brown or blackish coloration.

All authorities who have written on this subject are agreed that although remarkable recoveries take place by the proper use of E B I yet in a large series of cases a certain proportion prove refractory and there appears to be no object in persisting with this drug when once relapses have become established.

In a series of 134 cases the author has recorded ten relapses within a period of six weeks from the commencement of treatment with a return of symptoms and the demonstration of amœbæ in the stools. Three patients relapsed after as many as nine separate courses of E B I in which 30 grains or more had been given and there are reasons for believing that a strain of emetine resistant amœbæ had been produced.

E B I is not so effective in routine treatment for hepatic amœbiasis, nor can it always be relied upon to prevent the subsequent occurrence of an amœbic abscess, the author, in his series of 134 cases has seen re-admission of three cases with hepatic abscess (2.2 per cent).

Treatment with E B I is a great advance upon the original emetine method and some experiences can be quoted of which the following is an example —

A Naval ex seaman (1924) had contracted amœbic dysentery twelve years previously and though ill, had served throughout the 1914-18 war. He was then weak and emaciated and was passing blood and mucus stools swarming with amœbæ. On a 36 grain course of E B I he put on 8 lb in weight, and he subsequently improved so much in health that he was no longer recognizable as the same man.

E B I in therapeutic doses has no effect upon any other species of amœbæ which parasitizes man, except *Iodamœba butschlii* (see p. 534), nor has it any action upon other intestinal protozoa. It is more toxic to monkeys than it



is to man but it apparently eradicates a *histolytica* infection in these animals. C. Dobell and A. Bishop (1921) treated five tame monkeys with EBI by the mouth in order to study this effect. These monkeys were originally infected with *E. histolytica*, *E. coli*, *Endolimax nana*, *Enteromonas*, and *Giardia*. It was necessary to administer 60 mgm of EBI daily for a week to a macaque weighing 5 kilos in order to eradicate the infection, but this dose was toxic to four out of five animals.

Emetine does not, as a rule, cure acute amœbic dysentery in the cat, and it is pointed out that if this animal had been originally used to test the curative action of the ipecacuanha alkaloids, the therapeutic action of emetine in human amœbiasis would never have been discovered.

The modification of EBI—*emetine periodide* (EPI) ( $C_{22}H_{40}N_2O_4I_2$ )—was introduced by Martindale in 1923 and appears to be much less irritating than EBI. It is given in the same manner in capsules, each containing 2 grains, the maximum dose being 6 grains daily, combined with tablets of ox bile, 5 grains, three times a day. It has been claimed that vomiting and other phenomena frequently associated with EBI do not result with this compound.

The periodide of emetine contains 38.7 per cent emetine and 61.3 per cent iodine. Insoluble in water, it is readily soluble in alcohol, chloroform, ether, and other solvents. By analogy with other alkaloidal periodides, the alkaloid would split off from the other iodide atoms and leave the emetine molecule free.

Personal experience has shown that EPI is not so easily tolerated as was at first thought, nor does it eradicate the amœbic infection as efficaciously as does EBI, but to women, who are very sensitive to the latter drug, it may be given at night, in doses of 2 grains, when EBI is not well tolerated.

Another compound, *auremetine* (Willmore and Martindale), a compound of auramine—an aniline dye—and emetine, was introduced in 1926. It is a dark maroon powder, insoluble in water, and is a combination of the hydriodide and periodides of emetine and auramine—emetine 28 per cent, auramine 16 per cent, and iodine 56 per cent. It was claimed that it did not give rise to nausea or vomiting, and could be tolerated in doses of 1 gram in gelatine capsules, four times daily. This, also, has not been found better than EBI.

**Gavano** (Bayer) a derivative of ipecacuanha—probably cephaelin in combination with an organic acid—has been tried on account of its non-emetic properties. K. Akashi (1930) found that it cured ten cases of amœbic dysentery. P. N. Chopra and B. Sen tested this drug by the mouth in eighteen cases and find that it is less toxic than the emetine compounds, but the author in a limited trial found that it had no effect on the cysts of *E. histolytica*. It is administered in tablet form, the dose being one tablet three times daily for six consecutive days.

**Quinoxyl.** *Chiniofon* (B.P.), *Yatren*, *Dysentulin* (Germany), *Anayodin* (U.S.A.)—In 1921, P. Mullens and W. Menk introduced this substance for the treatment of chronic amœbic dysentery. Quinoxyl ( $C_8H_8O_4SN$ ) consists of oxyquinoline sulphonic acid in

combination with iodine (7 iodine-8 oxyquinoline-5 sulphonic acid) It contains 28 per cent of iodine with sodium bicarbonate, and is a yellow powder exhibited in the form both of pills and of retention enemata At first its use in dysentery was a pure experiment, but it now appears that it exerts a specific action upon the *E. histolytica*, as shown in culture tests V Nossina (1934) finds that the effective range is between pH 5.6 and 7.8 in a concentration of 1:5,000 P Muhlens and W Menk (1921) noted that this preparation possesses high bactericidal properties without destroying the tissues, and that at the same time it acts as a cell stimulant The first attempts were made with two specially resistant amoebic cases which, after months of emetine treatment, had undergone appendicostomy and cæcostomy In both instances an almost immediate clinical improvement took place

It is probable that a satisfactory and permanent result cannot be obtained when this drug is administered by the mouth Quinoxyl pills contain 4 grains (0.25 gm.), and it is recommended that as many as six should be given in a day In the author's experience this causes a considerable diarrhoea, is usually badly tolerated, and moreover fails to exterminate amoebic cysts If it is necessary to give it by the mouth, Muhlens has worked out the following scheme —

On the first day, three pills of 4 grains each (0.25 grammes) are given, from the second to the fifth day, two pills three times a day if tolerated, and on the sixth and seventh day, three pills three times a day The pills are best taken directly after a meal As an after cure lasting over three weeks, six pills should be taken daily on every fifth sixth and seventh day

Children as a rule tolerate quinoxyl and are given it in pills of 1 to 2 grains (A. G. Biggam, A. Halawani, and A. Ragab, 1931)

Soon after its introduction it became apparent that quinoxyl is more efficacious when injected into the rectum It is absorbed from the bowel, and the solution must be retained as long as possible It is subsequently excreted in the urine, where it can be demonstrated by the oxyquinoline test (green colour with perchloride of iron)

The bowel should first be washed clear of mucus by an enema consisting of 1 pint of 2 per cent sodium bicarbonate which is best given at 8 a.m. One hour later 200 c.c. (8 oz.) of a 2.5 per cent solution of quinoxyl in warm water is introduced through a stout rectal tube with a terminal opening, the patient being placed upon his left side with a pillow or sandbag under the buttocks The solution is slowly run in through a funnel, and the patient is encouraged to retain it as long as possible After lying on his left side for five minutes, he lies on his back for the same length of time, and finally turns to the right side, in order to assist the solution to distribute itself as evenly throughout the large intestine as is possible Usually, he can retain the solution from eight to ten hours, sometimes even longer Quinoxyl is excreted per rectum as a greenish liquid containing mucus and debris

derived from the bowel. Ten such treatments are necessary on as many successive days.

It is necessary to emphasize that quinoxyl should be given as a retention enema and *not* as a cleansing enema. There is proof that quinoxyl introduced into the rectum parcolates through the large intestine.

This was found in a patient who died suddenly from coronary thrombosis in February 1920. He had taken altogether 27 grains of E B I without any untoward symptoms being provoked and at the same time ten quinoxyl retention enemata. At autopsy quinoxyl was found coating the mucosa of the large intestine.

Though well tolerated, quinoxyl is apt to provoke diarrhoea, but this can be controlled by strict diet and rest in bed. That it exerts a direct effect upon the ulcers is proved by repeated sigmoidoscopic examinations which show rapid healing. The action upon *E. histolytica* is direct. H. Vogel (1927) found that a dilution of 1:100 killed all amoebae in cultures in three hours. 1:1,000 prevented multiplication in twelve hours. No toxic action has been ascribed to the drug, though rarely a rosary rash results.

As a result of investigations on the effects of quinoxyl given simultaneously by the mouth and by the rectum over a period of ten days in fourteen cases, the author (1925) with R. M. Morris concluded that the effects of this treatment were not always permanent, relapses being apt to occur, but that effects were specially good in those cases which had become resistant to emetine and emetine bismuthous iodide. As a result of this experience it was resolved to try out the combined effect of emetine bismuth iodide reinforced by quinoxyl retention enemata, a method which is now termed combined treatment.

**Combined treatment**—Combined treatment consists of injecting quinoxyl into the bowel (retention enemata) and at the same time exhibiting F B I at night so as to attack the amebic infection simultaneously. From observations by sigmoidoscopy it has been found that extensive amebic ulceration is present in the sigmoid colon and in the lower part of the rectum where it is improbable that F B I can exert full action, but that quinoxyl is specially effective for lesions in the lower bowel.

Experience has shown that it is unnecessary to give more than a total of 14–20 grains of E B I—that is to say, not more than 2 grains as an individual dose, the total treatment lasting ten days. It is most important to observe the preliminary precautions already described. In order to prevent emesis and nausea, 1 or 1½ grains of luminal should be given half an hour before the E B I—occasionally two tablets of allonal 10 grains *strict opni* (no enemas) or 10 grains of chlorotone are effective substitutes.

The following scheme has been drawn up of the combined treatment together with the diet recommended.

SCHEME OF DIETARY AND COMBINED TREATMENT FOR  
INTESTINAL AMŒBIASIS

On waking	Potassium chlorate mouth wash
7 a m	Tea and 2 oz milk
7 30 a m	One egg, buttered toast, cup of tea and 2 oz milk
8 a m	Sodium bicarbonate enema (2 per cent)
8 30 a m	Quinoxyl (2½ per cent) by rectum (7 oz)
9 a m	8 oz milk
10 30 a m	Juice of an orange, glucose ½ oz
12 noon	Liver soup, chicken or fish (boiled or fried), white sauce, toast and butter, custard or milk jelly baked apple
4 p m	Boiled egg, toast, butter, juice of one orange and ½ oz glucose, or grapes or ripe banana sponge fingers
5 p m	Quinoxyl retention enema voided
6 p m	Milk 8 oz, bath
9 30 p m	Sedative (luminal gr 1-gr 1½, chloretone gr 10 or nepenthe min 10)
10 p m	E B I gr 2
10 30 p m	Sleep

At the termination of the treatment the patient should be permitted two days' respite in order to recover from the strain of active treatment and to regain his "sea legs," for nearly always a sense of weakness or stiffness results.

Should a relapse of amœbic dysentery occur after this thorough treatment the course may be repeated, and the strength of the quinoxyl enema increased to 5 per cent.

The result of the combined treatment has been found most satisfactory. Subsequent relapses have been cured by further treatment on the same lines (See Table, p 190).

It might at first sight appear difficult to assess the ultimate value of the treatment described, on the grounds that the wide area from which the cases were drawn renders satisfactory follow up impossible. This, however, has been satisfactorily carried out and many have been periodically re-examined over a period extending from ten to fifteen years.

In the author's opinion this is the most efficacious form of treatment for intestinal amœbiasis yet devised. At the same time it would be going too far to say that it *never* fails. The main point is that the treatment must be conscientiously carried out with strict observance of detail.

For instance an official from Nyasaland contracted infection in March, 1933, when active forms of *E. histolytica* were present in a blood and mucus stool. He was subjected to a prolonged course of emetine injections and tablets of stovarsol taken by the mouth but became so ill that he was sent home to England. In September, 1933, he suffered from an acute amœbic hepatitis, with dysenteric stools still containing *E. histolytica*, whereupon he received an intensive course consisting of injections of emetine, retention enemata of quinoxyl, and bismuth by mouth, after which he was apparently cured. However, when he came up in November for re-examination, *F*

*histolytica* cysts were discovered in large numbers in the faeces. Again he went through an intensive course of treatment lasting nearly one month, but in place of emetine injections he was given large doses of auremetine by mouth, combined with retention enemata of quinoxyl. In January, 1934, as the stools were still positive, several new preparations were tried. In May, 1934, as he was suffering from diarrhoea with constantly positive stools, he came to London for treatment and received the combined emetine bismuth iodide (19 grains) and quinoxyl retention enemata in double strength after which he felt well and remained cyst free till the end of June. In July, they were again present in large numbers but circumstances necessitated his return to Nyasaland with instructions to take monthly courses of a quinoxyl derivative.

Two years afterwards, in July, 1936, he returned on leave and his stools were examined constantly over a period of three weeks, with a negative result. He is now apparently cured.

F W O Connor, T T Mackie and others have now published a number of cases in which they claim permanent cures of intestinal amoebiasis by the exhibition of *Anayodin*. O Connor (1931) describes this drug as being practically the same as quinoxyl. It is exhibited in the form of a pill of 4 grains, each pill containing 8 to 10 grains of sodium bicarbonate to increase the solubility, and 12 pills are given daily (i.e., four after each meal) for eight days. According to O Connor no other form of treatment is necessary. E Tonnard Neumann and F Valera (1931) have compared the actions of anayodin and quinoxyl and have been unable to distinguish any differences in therapeutic action between the two.

*Author's summary of ultimate results of treatment of 535 cases of amoebic dysentery (1941)*

I Anti amoebic treatment of 276 primary (previously untreated) cases		
EBI, EPI, quinoxyl and quinoxyl retention enemata		57
<i>Combined treatment</i>		
EBI + quinoxyl retention enemata		219
<i>Relapse rate, 1.4 per cent. Treatment repeated, all finally cured</i>		
II Treatment of 259 previously emetine injected cases in addition to inadequate amounts of EBI EPI quinoxyl stovarsol or carbarsone		
EBI EPI, 30-40 grs		100
Oral quinoxyl + retention enemata		17
Combined treatment		142
Relapse rate		7.7 per cent

It is therefore contended that previous intensive emetine treatment renders the disease more difficult to eradicate.

**Vioform** (iodochlorhydroxyquinoline) has been suggested as a substitute for iodoform and contains 37.5 per cent of iodine—a greater proportion than is present in yatren. H H Anderson, N A David and D A Koch (1931) found it was an effective amoebicide in monkeys infected with *E. histolytica*. Vioform is given by the mouth in gelatine capsules—each containing 0.25 gramme (4 grains) of the powder—three times daily for ten days. H H Anderson and A C Reed have reported upon sixty cases of amoebiasis treated orally with vioform, and three of these showed evidences of gastro intestinal

irritation According to these observers the drug is more satisfactory than quinoxyl

**Rivanol**, a derivative of acridine (2-ethoxy-8,9-diamino acridine lactate) was first recommended by O Urchs and F M Peter It is given as an enema in 1 : 2 000 solution 500-800 cm being injected at body temperature with the patient lying on his left side and afterwards adopting the knee elbow position Its action is said to be increased by the exhibition of sodium sulphate by the mouth The enema is retained as long as possible—for at least fifteen minutes—and it is said that a course of ten or more treatments are necessary This subject is dealt with by T Ronnefeldt (1931) and A G Biggam and M A Arafa (1930) Various opinions have been expressed as to the value of rivanol treatment Biggam and Arafa and other observers in Cairo believe that it is an excellent method for soothing the bowel and that it acts as an anti spasmotic but there is no proof that it is effective in healing amœbic ulceration Rivanol is also dispensed as Rivanolettes—tablets by the mouth in doses from 30 to 50 milligrammes daily Children receive a tenth of this dose

**Kurchi bark and its derivatives**—The alkaloid of kurchi bark (*Holarrhena anti-dysenterica*) a small deciduous plant from the Himalayas conessine has been found to exert some action upon the *E histolytica* in vitro *Kurchine hydrochloride* (Whiffen & Co) is the crystallized alkaloid from the bark and has the formula  $C_{21}H_{25}N_2$  It is given by the hypodermic route in doses of half to one grain and may also be given by mouth in the same quantities It is said to be far less irritating and toxic than emetine but it is questionable whether its effects are permanent *Kurchinetum bismithous iodide* was introduced by H W Acton and R N Chopra (1933) The drug is given by mouth in 10 grain doses without any deleterious effects apparently the same precautions are necessary as have already been described in the case of E B I It is said to be specially valuable in chronic intestinal amœbiasis as well as in cases of amœbic hepatitis The adoption of this drug is advocated on account of both the simplicity in its administration and the cheapness of its production Unfortunately the author has not seen permanent cures in cases of amœbiasis treated by this method in India who have returned to England

**Stovarsol, acetarsol, or spirocid** (acetyl oxy amino phenyl arsonic acid) was synthesized by Fourneau and introduced by E Marchoux (1922) for the treatment of amœbiasis in France It contains 27.2 per cent of organic arsenic Although it has definite value as an intestinal tonic and in the after cure of amœbic dysentery, it cannot be said that the French claims to its value as a reliable amœbicide have been fully substantiated On account of its simplicity stovarsol has been extensively used in treating mild cases of amœbiasis and carriers and according to E F Craig in his practice 60 per cent of infections were eliminated after one course of treatment He has however had to abandon its use on account of its toxic propensities

It has been customary to exhibit this drug in doses of 4 grain tablets (0.26 gramme) twice daily for ten days as an after treatment and in carriers who for various reasons cannot undertake vigorous courses of treatment It is necessary to emphasize that there may exist a definite

idiosyncrasy to stovarsol. Its action on the *Entamoeba* is due to the arsenic it contains and cases of arsenical poisoning, sometimes even fatal have followed. On no account should patients be allowed to take the drug without strict instructions regarding its possible toxic effects. Optic atrophy is possible from gross overdosage.

One of the most common forms of stovarsol poisoning consists of an urticaria like rash on the face, neck, and trunk, together with pyrexia and sometimes adenitis, it so closely resembles German measles that two cases in the author's practice were sent to a fever hospital and other instances have been reported in the literature (F. D. Annesley 1928). There is also a curious form of delayed stovarsol poisoning. H. C. G. Semon (1932) reported such a case in which toxic symptoms were noted some days after administration. Injections of sodium thiosulphate have been found useful in relieving this toxic dermatitis (J. Morgan 1926).

Treparsol, an arsenobenzolic derivative of the salvarsan type, has been used in the treatment of amoebiasis in the same manner as stovarsol and has the same disadvantages though it is said to be more rapidly eliminated. P. W. Brown (1928) found it gave excellent results when combined with emetine therapy.

Carbarsone ( $H_2O, 1s_2C_6H_4NHCONH_2$ ) as originally prepared by Lihlich is 4 carbamino phenyl arsonic-acid containing 28.8 per cent of arsenic and is allied to tryparsamide and stovarsol. In America there have recently appeared a number of papers advocating the administration of this drug in chronic intestinal amoebiasis. A. C. Reed, H. H. Anderson, N. A. David and C. D. Leake (1932) advise for an adult 0.25 gramme twice daily for ten days given in gelatin capsules (pulvules) by the mouth. It is claimed that the drug is clinically non-toxic in effective doses and it may conveniently be administered orally without interfering with the patient's usual mode of life. Its therapeutic action is due to arsenic and it is less toxic than stovarsol. Nevertheless this drug should be administered only under supervision. (Recently a fatal case of arsenical poisoning has been reported after its use (E. Epstein 1936)). The author's experiences of the end result of carbarsone treated amoebic dysentery have not been favourable. One such case may be quoted.

A patient was referred as in a particularly acute attack having taken two pulvules (8 grains) daily for one month nevertheless many active amoebic ulcers in which amoebae were demonstrated, were seen in the rectum and sigmoid by sigmoidoscopy. He was subsequently cured by the combined treatment.

Both stovarsol and carbarsone may be administered in the form of retention enemas of 2 grammes in 200 c.c. of warm sodium bicarbonate solution.

Amibarson is a new compound with a chemical composition similar to carbarsone and with a similar action (P. N. Chopra, B. Sen and G. Sen 1935).

**Bismuth subnitrate**—For many years W. E. Deeks (1914) in Panama, advocated large doses of bismuth salts given by the mouth, claiming that little, if any, of the bismuth was absorbed. As much as 180 grains mechanically suspended in a tumblerful of milk or water, every three hours night and day, were exhibited in severe cases. Very occasionally some untoward effects, such as cyanosis and forcible action of the heart, have been observed, and these have been ascribed to impurities. During the first ten days strict dietary is necessary, after which a non-irritating diet must be maintained for two or three months.

There are not many advocates of this strenuous bismuth therapy at the present day. Probably it merely masks the symptoms of an acute attack, but since such administration tends to convert the acidity of the colon contents to alkalinity, it may render the medium incompatible to *E. histolytica*.

**Chaparro Amargosa**.—This is an extract made from the bark or leaves of a Mexican plant, *Castela nicholsoni*, and has been extensively used in that country. Five teaspoonfuls are suspended in 8 ounces of boiling water for a quarter of an hour, the decoction is allowed to cool and is strained before use. It may be given by the mouth (but the taste is acrid), three teaspoonfuls a day, or by means of an enema of 12 ounces. Treatment should be continued for ten days.

**Simaruba**—Made from the bark of plants of the genus *Simaruba*, this has long had a reputation in the treatment of amœbic dysentery. It contains a principle similar to or identical with that of Chaparro. A teaspoonful of powder is infused in the manner described above, and it is given in the same dosage.

**Kho-sam**.—This also is a native cure for dysentery. Prepared from the seeds of *Brucea sumatrana* (*Simarubaceæ*) it has been recommended by French workers in Cochin China, but there is no evidence that it contains any active principle.

**Uzara**, of which the active principle is uzarine, is the name for a native remedy derived from an African plant of the family *Asclepiadaceæ*. It is given in the form of a tablet. This drug appears also as a proprietary preparation—*Panzaron*—that has been recommended by German workers.

**Salvarsan** has been recommended by French workers for refractory cases of intestinal amœbiasis, administered intravenously, orally, or rectally. P. Ravaut has recommended neosalvarsan injections combined with emetine and it certainly does appear to be efficacious in those cases in which a history of syphilitic infection can be obtained.

**Bael fruit** (*Aegle marmelos*)—This is a large globose fruit with a hard woody rind and an astrigent yellow pulp. The pulp contains sixteen cells each lodging an oval seed surrounded by transparent mucus with a turpentine-like flavour. Two fruits can be given in the course of one day. The soft pulp is scraped out of the shell by a fork and should be well mixed with sugar and cream and eaten in small amounts with each feed of milk, or it may be given in an infusion in the form of bael fruit tea. It is an adjuvant to the treatment of amœbic dysentery.

**Ravaut's paste**, introduced by P. Ravaut and Charpin in 1919, consists of powdered charcoal, subnitrate of bismuth, syrup and glycerin, 100 grammes of each and powdered ippecacuanha 4 grammes. The dose is about 1 drachm three times daily. Le Noir and M. de Fossey (1922) found that when combined with intravenous injections of salvarsan (0.3 gramme) favourable results were



obtained Ravaut's paste is usually given for a course of twelve days. It has been used a good deal in France.

**Drugs used for special symptoms.** *Secondary diarrhoea*—This diarrhoea occurs sometimes in a bowel which has been greatly damaged by amœbic ulceration, and various enemata have been advocated—

- |       |                     |                      |
|-------|---------------------|----------------------|
| (1) R | Quinin dihydrochlor | 10 gr (0.65 grm)     |
|       | Acid boric          | 2 drachms (7.75 grm) |
|       | Aq ad               | 2 pints (1,336 c c)  |

To be given at body temperature

- |       |                   |                 |
|-------|-------------------|-----------------|
| (2) R | Acid tann         | 150 gr (10 grm) |
|       | Quinin hydrochlor | 15 gr (1 grm)   |
- To be dissolved in  $1\frac{1}{2}$  pints (1 litre) of warm water (If pain is caused use at half strength)

*Post dysenteric colitis*—A kind of mucous colitis is frequently seen after amœbic infection. This must be treated on the principles laid down for the treatment of that disease in Chapter XXIII.

*Post dysenteric constipation*—Obstinate constipation may often set in. The usual oily preparations such as liquid paraffin, petrolagar, isogel or agarol may be employed, castor oil may be necessary, and salts also may be beneficial. The following mixture is recommended.

- |   |            |          |
|---|------------|----------|
| R | Ferr sulph | 3 gr     |
|   | Liq arsen  | 3 minims |
|   | Inf aloes  | 1 oz     |

One ounce three times a day

**Proof of radical cure**—It is by no means easy to prove that a patient is entirely free from amœbic infection after curative treatment, owing to the fact that, during treatment the parasites, whether active forms or cysts, disappear from the stools. Even in uncured cases cysts do not re-appear for three or four weeks after cessation of treatment. Clinical relapses have to be considered as well as parasitical, i.e., the re-appearance of the parasite in the stools in the absence of obvious clinical symptoms. It used to be considered that, if the stool was examined daily for three weeks without discovering amœbic cysts, the patient could be considered cured, but at present it is probably more practical to control treatment by periodic sigmoidoscopic examinations.

#### ILLUSTRATIVE CASES

##### (1) *Duration sixteen years*

P.H.C., 70, twenty years in India. First attack of amœbic dysentery 1923, treated by emetine injections, second attack in England seven years later. Third attack 1939, owing to loss of weight, diarrhoea, blood and mucus stools, suspected of carcinoma. Sigmoidoscopy suggested amœbic ulceration, confirmed by scrape preparations. Faeces contained large numbers of *E. histolytica* cysts. Combined E.B.I. and quinoxyl retention enema treatment for 10 days. Since then

bowels perfectly normal, no further symptoms Increase in weight five pounds

(2) *Duration twenty-one years*

Mrs E W, 64, spent six weeks in Bombay and ten days in Colombo in 1913, never in tropics since Ever since has had chronic diarrhoea In 1929 had a liver abscess from which she recovered, in 1931 suffered from acute cholecystitis, gallbladder with over 1 000 small calculi removed In 1934 streptococcal abscess of right lung Faeces examined October, 1934, numerous active *E histolytica* Routine combined treatment—E B I and quinoxyl for 10 days—well tolerated Free from infection since

(3) *Duration thirty one years*

D B B, 56, lived 21 years in India and 2 in Mesopotamia In 1910 amoebic dysentery with liver abscess (aspirated—two operations) Seven years later recurrence of amoebic dysentery treated by emetine injections, after which periodic attacks of diarrhoea Last 22 years in England In June, 1941, sudden acute attack of diarrhoea with tenesmus, carcinoma suspected on account of wasting and cachexia Sigmoidoscopy revealed amoebic ulcers and faeces contained *F histolytica* cysts Combined E B I and quinoxyl treatment resulted in cure Put on weight, normal stools since

(4) *Amoebic dysentery in boy of 15, duration 10 years, possibly longer*

A P B, 15½, born in India, lived there till 5½ At seven months had first attack of dysentery (? amoebic) At 5 relapse, treated by emetine injections Intermittent attacks of diarrhoea subsequently for 6 years Diarrhoea recommenced at 13, examined in August, 1941, was then severely ill with emaciation, anaemia and abdominal pain Blood and mucus stools with active *E histolytica* and Charcot Leyden crystals Combined E B I and quinoxyl enemata for 10 days Since then has kept perfectly well, returned to school and plays vigorous games

(5) *Duration 28 years appendicostomy*

W C, 61, first attack of dysentery in S African war in 1901 Seen in February, 1929 During 28 years suffered intermittently with diarrhoea, blood and mucus In 1929, on supposition that he was suffering from ulcerative colitis appendicostomy For 10 years continuously he irrigated himself daily through the wound In faeces cystic and precystic forms of *E histolytica* Combined E B I and quinoxyl enemata for 10 days Appendicostomy closed Reported June, 1941, in good health, no return of symptoms

(6) *Duration 24 years*

V C, 43, Danish correspondent, resided one month in N Borneo in 1907 where he had attack of dysentery On return to Copenhagen had chronic diarrhoea for 24 years In 1910 amoebic dysentery diagnosed, lavage and diet treatment unsatisfactory In March, 1931, averaged six stools daily *E histolytica* cysts found Loss of weight 20 lbs

liver enlarged, infiltration of sigmoid and large intestine Combined E B I and quinoxyl retention enemata Reported regularly since in good health

(7) *Duration 11 years, appendicostomy*

L P, 84, contracted amœbic dysentery in Burma in 1921 Emetine injections Returned to England 1923 Case is remarkable on account of resistance to emetine and E B I Had three separate courses of E B I (30 grs) in hospital Acute relapses on each occasion within 14 days Finally prolonged stovarsol course Regarded as incurable, appendicostomy performed and lavage with ipecacuanha solution for 8 years Seen in February, 1932 Active *E. histolytica* in discharge from appendicostomy and in faeces Combined E B I (grs 22) and quinoxyl enemata, also quinoxyl irrigations through appendicostomy After 5 months appendicostomy wound closed, no dysentery since Subsequently had ureteric calculus, passed *per urethram*

**Diet.**—The problem of diet in the convalescent treatment of amœbic dysentery is rather a controversial subject In the author's opinion, when efficient cure of intestinal amœbiasis has been attained the need for strict dietary does not arise, but for the present it is safer to adhere to a judicious dietary for at least one month from the cessation of active treatment The main point is to avoid too much starch and fat Alcohol, except in small quantities, appears to predispose to a relapse

The author advocates the following dietary for four weeks after active treatment

<i>Permitted</i>	Porridge, eggs, fish (haddock, plaice, cod, sole, or whiting either boiled or fried), chicken (boiled or roast), rabbit, game (pheasants, partridges, pigeons etc) Milk puddings (rice, sago, semolina, ground rice), toast, rusks, biscuits, brown bread, Vita bread Vegetables (spinach, vegetable marrow, cauliflower, brussels sprouts, young carrots or young turnips) Stewed fruit (pears, peaches or prunes) baked apples, bananas, grapes, oranges, grape fruit plain cakes, fruit jellies, custard pudding or plain puddings Red meat—such as underdone beef or mutton—is advocated for lunch and such dishes as tripe, brains, and sweetbreads are also permitted Beverages—light wine or claret
<i>Not permitted</i>	Cheese new bread, potatoes, fats, suet puddings, rich cakes, pastry of all kinds coarse fruit and vegetables (turnips or carrots, cabbage) pickles, sardines and preserved fish. Beverages—spirits, beer or stout

**Resistant cases**—Formerly—even within the last five or six years—resistant cases of intestinal amœbiasis were frequently encountered, but at present it is generally agreed that amœbic lesions of the large intestine yield readily to emetine and quinoxyl treatment so that there is no justification for resort to surgical measures, such as appendicostomy, as in bacillary dysentery, with the object of washing out the bowel Indeed, recent experience goes to show that such measures should never be adopted, except as a last resort

## THE SURGICAL ASPECTS OF AMŒBIC DYSENTERY

Although the surgical complications of amœbiasis—other than liver abscess—play a considerable part in tropical practice, yet this important aspect has received scant attention in textbooks. It has already been pointed out that amœbic dysentery may simulate many other diseases. Symptoms may resemble those of hæmorrhoids, carcinoma of the rectum or the cæcum, tuberculous enteritis, intestinal obstruction, gangrene of the rectum and, in the case of amœbic hepatitis, cholecystitis and ascending pyelophlebitis. Acute amœbic hepatitis may simulate perforated gastric ulcer, appendicitis, also, may readily be mimicked for instance, by amœbic typhlitis, by perforation of the cæcum, or even by acute hepatitis.

Perforation of the cæcum may take place suddenly, or the process may be insidious, accompanied by formation of a localized abscess. Perforation of any portion of the colon may also occur, causing general peritonitis, localized pericolic, or pericolic abscess. Perinephric abscess due to localized perforation of the ascending colon has also been recorded. Acute œdematous inflammation of the colon or extensive sloughing of the intestinal wall may accompany this complication, while cicatrization and stenosis of the colon may give rise to obstruction. Hæmorrhoids are not infrequently a complication of amœbic dysentery and proctitis with rectal stricture and fistulæ may occur\*.

A. E. Sitsen (1927), in an extensive experience of over 3,400 cases and autopsies in Java, has found that an extension of the inflammation through the bowel wall often occurs, and gives rise to peritonitis with adhesions, sometimes also perirectal abscesses and recto vaginal fistulæ may result.

*Perforation of the colon*—Acute perforation is accompanied by faecal flooding; the symptoms indicating this catastrophe are sudden onset of abdominal pain with vomiting, collapse, rising pulse-rate, and distension and rigidity of the abdomen. In a profoundly toxic patient the symptoms may not be so dramatic, and perforation may only be suspected when there is spreading abdominal tenderness and distension. If retroperitoneal perforation occurs, or if adhesions have formed round the attenuated area of the bowel wall abscesses may gradually form. Usually this gives rise to local pain and tenderness, most commonly in the right iliac fossa where it may closely resemble appendix abscess.

The treatment of amœbic perforation is a surgical procedure, although usually these cases are recognized too late. C. C. Choyce recorded two cases of successful suture of dysenteric ulcerations during the 1914-18 War (Private communication). In one there was a localized abscess shut off by adhesions, which was opened and drained. In the other a

\* Z. Cope (1920) records operating upon 12 cases of perinephric abscess of which four had a history of previous dysentery and two had amœbic cysts in the faeces. He also records cases of proctitis in which amœbæ have been demonstrated in the resulting fistulæ.

leak was found in the terminal portion of the ileum which was sutured and with free drainage the patient recovered. If the perforation cannot easily be closed, the affected loop should be drained extraperitoneally.

In *amœbic typhilitis* a tender swelling in the right iliac fossa is usually found together with slight fever, vomiting and nausea. As O Barry and S. J. Crump (1916) remarked, the surgeon will do well to weigh carefully the history of an attack of chronic dysentery before deciding on the immediate abdominal operation, and once more it must be emphasized that, in every country where amœbic dysentery is endemic the surgeon should have the faeces examined for amœba or cysts before deciding upon operation.

In *amœbic appendicitis* the appendix is usually involved in common with the rest of the caecum and seldom gives rise to definite diagnostic signs and symptoms. The caecum is generally found to be œdematous. True amœbic appendicitis has to be distinguished from amœbic perityphilitis and also from amœbic dysentery in which ulcerations are limited to the caecum. It is important to note that in sulterian malaria a condition may arise which closely simulates it. Z. Cope advocated the thigh rotation test as useful in determining whether tenderness per rectum is due to ulceration of the pelvic colon or to a perforated appendix.

*Thrombosis* of the portal vein as a surgical complication of intestinal amœbiasis has been described by A. E. Sitsen (1918).

*Fulminating amœbic dysentery*—The dysenteric process is sometimes so acute that large portions of mucous membrane become gangrenous and slough with spread of infection through the bowel wall into the peritoneal cavity. In this condition the surgeon may be asked to operate either to provide an opening for washing out the colon from above or to divert the intestinal contents and thus give the colon a rest. For the former purpose appendicostomy or cœcostomy is the operation of selection, for the latter ileostomy.

As a general rule surgical interference in intestinal amœbiasis is strongly contra-indicated. Whenever it has been somewhat recklessly undertaken disaster has resulted. Thus was the experience during the Chicago epidemic of 1933-34. In the author's experience when a colostomy has been undertaken in amœbiasis on the mistaken conception that the symptoms are those of carcinoma, amœbic ulceration is accentuated rather than retarded. In September 1937 the author had such a case under his care—an ex-soldier from India, twenty-five years of age (see p. 250). Colostomy had been performed to relieve symptoms as rectal ulceration had been mistaken for malignant disease. Amœbic infection of the skin had resulted, the colostomy wound had become offensive and septic with brawny infiltration of the abdominal parietes. Response to emetine therapy was miraculous.

It is only in exceptional surgical complications that appendicostomy and cœcostomy are indicated. Uncontrollable hæmorrhage for instance may be an indication for cœcostomy for purposes of lavage and the

application of styptics. Subsequent to any operative measures the patient should undergo a curative course with E B I and quinoxyl.

In the *hyperplastic form* of amœbiasis R. W. Runyan and A. B. Herrick have found it necessary to excise the diseased portion of the colon and to perform end to end anastomosis. A condition simulating tumour, produced by enormous thickening of the bowel-wall, was encountered in four cases; in one it was primarily diagnosed as a caecal tumour. It is usually considered safest to resect the diseased portion by Paul's method. Intestinal obstruction due to an amœbic granuloma may necessitate a short circuit operation.

**Immunity.**—Although there is nothing definite known about immunity to infections with *E. histolytica*, such evidence as we possess may be summarized. It has generally been supposed that a previous infection with *E. histolytica* confers no immunity, since a person cured of an amœbic infection appears to be just as liable to a fresh one. This has been found to be the case, certainly, in experiments on animals. Immunity to infection with *E. histolytica* is probably dependent primarily upon the resisting power of the host. These are the clinically observed facts, while a considerable amount of tentative work on immunity reactions of amœbiasis has been carried out in laboratory animals (see p. 154).

**Prophylaxis.**—The measures adopted to prevent infection with *E. histolytica* are practically the same as those already described for bacillary dysentery, and depend in the first place upon efficient sanitation and measures directed against the house-fly which may act as a carrier of amœbic cysts. It must be especially insisted that in the tropics, raw vegetables, lettuce, fruits, and foods which have been exposed to the air and possibly contaminated by human excreta, must be avoided. The prevalence of intestinal amœbiasis in heavily cultivated districts is undoubtedly due to the prevailing custom of fertilizing with human night soil. The cysts of *E. histolytica* can survive in a moist medium and there is considerable evidence that the disease is in the main water borne, thus in large communities, the problem resolves itself into the provision of a pure water supply.

The question of dealing with human carriers of *E. histolytica* cysts is difficult. It is probably advisable that, in the tropics, where a large number of native servants are employed, faeces should be examined periodically for cysts of *E. histolytica*, and no cyst carrier should be employed as cook, waiter or mess orderly. Wherever possible, infected individuals should be treated with emetine-bismuth iodide and the source of infection removed.

As C. F. Craig (1935) rightly points out, amœbiasis must be regarded as a public health problem in those countries where it is endemic, as it has been proved to be in parts of the United States. The evidence shows that it is present in parts of that country, and that 5–10 per cent of the population harbour *E. histolytica*.

Successful prevention and final eradication of amœbiasis depend upon general sanitation, pure water supply, and protection of food from flies. Efficient sterilization of drinking water is most necessary. This cannot be effected by chlorination but is more efficiently done by filtration (B. K. Spector, J. R. Baylis and O. Gullans 1934). The former method does not destroy the cysts of *E. histolytica*.

For the recognition of the disease in infected persons and of carriers of amœbic cysts, a thoroughly trained laboratory personnel, well versed in the differentiation of *E. histolytica* from other species of amœbæ and from intestinal flagellates, is necessary, and such an efficient staff is not always easy to obtain.

## CHAPTER XIV

### AMŒBIASIS (*continued*) : SECONDARY AMŒBIASIS\*

In secondary amœbiasis the liver is the organ most frequently affected, resulting, as a rule, in amœbic hepatitis or in hepatic abscess.

**Amœbic hepatitis or hepatic amœbiasis**—Acute amœbic hepatitis may supervene at any time during the course of amœbic infection in about 5 per cent of cases. It may come on while symptoms are acute or it may appear as a 'bolt from the blue' during a remission of the disease. It may be accompanied by alarming symptoms and is usually preceded by a rigor. The patient complains of dyspepsia, acute

September, 1937

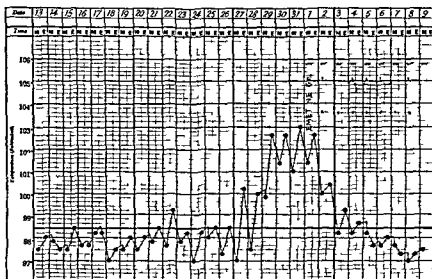


Chart 3—Amœbic hepatitis occurring during chronic amœbic dysentery. Note immediate response to emetine therapy.

precordial pain and a heavy sensation over the hepatic area. Sometimes when the onset is not quite so acute, he may become conscious of a sharp stabbing pain over the liver, accentuated by any jarring movement. The temperature may rise to 103° or 104° F. The face is flushed, the tongue furred, and the patient obviously in great pain. The liver itself is usually greatly enlarged—the lower border may

\*The historical aspects of this subject have been ably set forth by W. A. B. Karunaratne (1940-1).



project for more than a hand's breadth below the costal margin—and extremely tender. Pain referred to the right shoulder area is also frequently present. Onset of hepatitis is accompanied, as a rule, by exacerbation of the dysenteric symptoms and diarrhoea. The pulse is rapid and dicrotic and profuse diaphoresis is common. A distinctive feature is a considerable leucocytosis 20,000–30,000.

Acute hepatitis may subside in three or four days without active treatment. The condition yields to emetine therapy (Chart 3), and the liver diminishes rapidly after incision and operation, or after withdrawal of blood through an aspirating syringe (hepatic phlebotomy) (A. Degorce, 1914). Apparently amœbic hepatitis is due to a massive invasion of the liver by active *E. histolytica* (see p. 241). According to Z. Cope (1920) and also to the author's experience, it may develop four years or more after cessation of intestinal symptoms.

A nice point in differential diagnosis is the distinction between acute amœbic hepatitis and acute cholecystitis—by no means always easy. In cases of doubt, assistance may be sought in the marked leucocytosis which is associated with hepatic amœbiasis, its connexion with previous recognized amœbic infection, and the absence of any of the secondary signs of gall bladder infection such as a positive Van den Bergh reaction and bile pigments in the urine.

The association of amœbic hepatitis with jaundice is very rare and when there are signs of obstructive icterus, then amœbiasis can be ruled out, but toxic jaundice may occasionally accompany hepatic amœbiasis.

The author has treated two genuine cases of this condition, one from China, the other from Sierra Leone. The liver signs were typical, the urine contained bile salts and bilirubin and the stools *E. histolytica* cysts. This was associated with typical pyrexia. The blood-serum contained 4 indirect Van den Bergh units. Response to emetine and E. B. I. was satisfactory.

Z. Cope has discussed its differentiation from acute appendicitis in those cases in which the pain is referred to the right iliac fossa and has drawn attention to the almost miraculous effect of emetine under these circumstances.

Chronic amœbic hepatitis, that is, a general enlargement of the liver in the absence of exacerbations, is occasionally met with and may be confused with the enlarged liver of heart disease, malaria, or possibly, hypertrophic cirrhosis. Chronic amœbic hepatitis may also be the precursor of hepatic abscess. It usually resolves quickly after the injection of emetine.

Occasionally relapsing cases of acute amœbic hepatitis with multiple rigors may occur. The following is an illustrative case—

An officer, who had returned four years before from service in Mesopotamia, was seen in November, 1927. His illness had lasted four months and was characterized by multiple rigors with pyrexia reaching 105° F. Sometimes two occurred within twenty-four hours. There were no signs or symptoms pointing to any particular organ of the body, save that an enlargement of the

liver became apparent as the disease progressed. The leucocytes numbered as high as 30,000, with 80 per cent of polymorphonuclears. Faeces contained *E. histolytica* cysts. The fever ultimately resolved after intense anti amœbic treatment over a period of six weeks. The case was further complicated by the appearance of intramuscular abscesses due to quinine injections given by his former medical attendants under the mistaken impression that the rigors were of malarial origin.

**Hepatic abscess (Liver abscess, Amœbic abscess of liver)**—There can now be no question of the existence of an intimate relationship between intestinal amœbiasis and liver abscess, as numerous and well authenticated statistics go to prove. Hepatic abscess is, however, not always associated with obvious clinical dysentery, therefore the absence of a positive history of amœbic infection, or of diarrhoea, does not rule out the possibility of an amœbic liver abscess.

The association of intestinal symptoms with liver abscess has long been recognized, but it cannot be said that, until comparatively recently, information on the subject was either well defined or precise. Since 1887 it has been generally accepted that tropical liver abscess is, in fact, but a complication of intestinal amœbiasis. The actual invasion of the capillaries of the bowel wall by amœbæ and their subsequent transportation to the liver was first observed by H. F. Harris (1898). It is especially likely to attack Europeans, in contra distinction to natives of those countries in which amœbiasis is endemic. In the Indian Army in 1894 the proportion of deaths from liver abscess to the total mortality was estimated, in native troops, at 0.6 per cent, whereas in European troops it was 7.4 per cent. It is unquestionably true that amœbic abscess of the liver was much more frequently encountered in former times than at the present day. According to Sir I. Fayrer, the proportion of deaths from this cause in 1850-79 among British troops in the main strength of 57,742 was 2.19 per 1,000.

In strong contrast to the incidence and frequency of liver abscess and hepatitis in the tropical regions of the Far East, is the comparative infrequency in the West Indies and South America.

Undue consumption of alcohol was formerly considered a potent predisposing cause, thus in forty cases of liver abscess, E. J. Waring noted intemperance in 67.5 per cent. Few authorities at the present day, however, consider that alcoholic excess is such an important factor.

The relationship between amœbic dysentery and liver abscess was worked out by L. Rogers in India, 1901-10. There he showed that there was a definite ratio between the admissions of these diseases in British Army Hospitals. It is known that extensive amœbic ulceration of the bowel may exist in the human body without causing any obvious signs or symptoms, and Rogers (1913) proved that in this condition amœbic ulcers, either active or passive, are almost invariably found in the cæcum or in the ascending colon (sixty three cases, with dysentery findings in 90.5 per cent). Liver abscesses have been found frequently in association with fatal amœbic dysentery (C. F. Craig (1934) 33 per

cent, A. E. Sitsen (1927) 10 per cent, A. C. Clark (1925) 51 per cent) Chauffard (1892) has epitomised as follows—"The more frequent, grave and persistent dysentery is in a country, in like proportion will suppurative hepatitis be frequent grave and persistent" In the great majority of cases dysentery antedates the onset of the abscess—it may be for twenty years or longer, as in the cases cited by G. C. Low (1916), the author, and others

*Ætiology*—Liver abscess is apparently likely to occur in about 2-5 per cent of amœbic infections in Europeans, but to a much smaller degree in natives of the endemic zones\*

As a general rule, liver abscess occurs in those Europeans who have long been resident in the country, it is not a disease of the new comer

It is well known that European women in the tropics, though as frequently subject to amœbic dysentery as European men, rarely suffer from liver abscess. The disease is most common between the ages of twenty and forty, and it rarely occurs in children, the youngest case in the author's series being eleven years of age. A. G. Biggam (1932), however, in Cairo, reported an amœbic liver abscess in a child of three months

P. Huard and J. Meyer May (1936) record a series of 150 cases in which liver abscess occurred in 137 men, 12 women and one child, 66 of the patients were Europeans, and 84 native Tonkinese

J. M. Tao (1931) in China in 1,000 cases of amœbic dysentery, found liver abscesses in 1.8 per cent, C. F. Craig, in Europeans in America in 745 cases, slightly over 5 per cent

#### PATHOLOGY OF HEPATIC AMŒBIASIS

Probably the liver becomes invaded by *E. histolytica* via the portal vein. It has already been stated that in sections of the bowel, amœbæ may be found multiplying in thrombosed veins and it is thus obvious how they may be swept by the blood stream into the liver

Amœbæ were originally found in portal emboli by Councilman and Lafleur, and they have been traced in blood clots for the whole length of the portal system to their distribution in the interlobular veins (W. C. Brown, 1910). The majority probably die out owing to the protective influence of the healthy liver cells. C. M. Wenyon (1913) has demonstrated amœbæ in the mesenteric lymphatic glands in these cases

F. Sambuc (1913) suggested that anastomosis of lymphatic vessels between the pleura and the liver is responsible for the frequency of pleurisy in hepatic abscess, according to this view pleuritis may be divided into those which are the result of direct extension and those which are of metastatic origin. Councilman and Lafleur (1891) originally demonstrated amœbæ in the exudate on the surface of

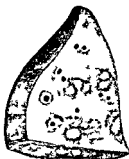
\* Probably the estimates which placed the incidence of amœbic abscess at 20 per cent., e.g. in Councilman and Lafleur's series in 1891 were exaggerated. A. Davidson writing in 1907 states that 8.5 per cent of those suffering from amœbic dysentery developed liver abscess

the liver, but there is no evidence that they can enter by the peritoneal surface or by the bile ducts. Ch. Dopter and K. Deschiens (1938) have, in fact, shown that the presence of bile salts in culture media retards the development of *E. histolytica*. The capacity possessed by the liver for regeneration is remarkable. The liver outside the abscess area may have a normal appearance or may show varying degrees of congestion.

The liver of an infected person is subject to constant attack by invading amœbæ. If, however, they are unable to obtain a footing they soon perish, as the hepatic cells appear to be able to arrest further multiplication of *E. histolytica*. Unless they are able to produce large areas of necrosis hepatic abscess does not ensue.

The production of numerous small necrotic areas a few millimetres in size, containing gummy pus with actively dividing forms of *E. histolytica* results in amœbic hepatitis (Fig. 25) and may not necessarily precede a genuine hepatic abscess.

Fig. 25 — Miliary necrotic foci in liver in acute hepatic amœbiasis with portal distribution of the entamœbæ



P H M B

G. B. Bartlett (1917) found hæmorrhages in the central zones of the liver lobules and insular cirrhosis has been noted by other observers. Both this and necrosis are the results of metabolic and chemical toxins. In sections through the wall of an acutely spreading abscess the amœbæ may readily be seen in the blood vessels. This appears to be the result of a much more gradual and insidious process though the factors which govern the behaviour of amœbæ in the liver and the subsequent pathological effects brought about by their presence are not entirely understood. When once amœbæ have become established they multiply as they do in the intestinal wall causing coagulation necrosis and formation of abscess cavities. Several primary centres then coalesce the cavity becomes occupied by what is usually termed liver abscess pus which is really gummatous matter consisting of dead liver cells in all stages of disintegration but where this process is not so complete, washleather like sloughs are formed. Liver abscess pus is the result of breakdown of the liver cells and not of suppuration and appears as a reddish brown or chocolate coloured substance resembling anchovy sauce usually sterile in the bacteriological sense.

Liver abscesses are as a rule solitary although they may be multiple ranging through both lobes of the liver the latter being commoner than was formerly believed and constituting about 30 per cent of all cases C D de Langen (1936) stated that only rarely are there more than two In H J Waring's series (1897) abscesses were single in 61.5 per cent double in 11.5 per cent and multiple in 27 per cent In 199 cases Huard and Meyer May (1936) found that in 102 cases the abscess was situated in the anterior portion of the right lobe, and in 87 in the posterior portion They found a proportion of 137 cases of single to 13 of multiple abscess

L Sambuc of Cochinchina in a classification of eighty seven cases of liver abscess (1913) found that in —

56 cases there was	1 abscess
11	were 2 abscesses
10	3
2	4
1 case	5
1	8

According to L Rogers (1913) in India in 70 per cent of cases the abscess is single Among thirty eight cases of more than one abscess two were found in 44.7 per cent three in 20.3 per cent four in 18.4 per cent and over four in 10.6 per cent

The left lobe is rarely infected the Spigelian lobe even more rarely In ninety five cases of amœbic abscess observed at autopsy H C Clark (1925) found fifty three located in the right lobe (55.7 per cent) sixteen in the right and left lobes (16.8 per cent) fifteen in all lobes (15.7 per cent) and eight in the left lobe (8.4 per cent) In C F Craig's series of twenty four cases (1935) he found nine cases presenting single and fifteen multiple abscesses Of nine fatal cases five were in the right and three in the left lobes and one in the lobus Spigelii Out of 633 cases collected by Roux (1860) 70.8 per cent were in the right lobe 13.3 per cent in the left In 756 autopsies (Hoppe Seyler 1903) 53 were on upper surface 39 anterior 46 inferior 47 right border 36 on posterior surface and 67 in the interior

The following statistics are given by various authorities —

	<i>Right lobe</i> <i>Per cent</i>	<i>Left lobe</i> <i>Per cent</i>
Huard and Meyer May	92	8
Pontan	97	3
Chatterji	78	22
Sir L Rogers	88	12

L R Cleveland and E R Sanders (1930) appear to have proved in their experimental work on cats that in these animals amœbæ introduced into the liver fail to set up pus formation unless bacteria are also present These workers favour the idea that some symbiosis exists between the protozoan and bacteria

A typical liver abscess increases in size until it may involve nearly the whole organ (A I Ludlow 1926) and the largest may attain the size of an average coco nut. A whole lobe or even the entire organ may be converted into a bag of pus the capsule forming the sole wall. Waring has recorded two cases in which a gallon of pus was found. As it enlarges so the cavity continues to fill with cytolyzed liver cells, necrotic tissue and blood the process advancing so rapidly that no pyogenic membrane is formed. At this stage the pus may sometimes become secondarily infected with micro organisms such as *Bacillus*

Fig 26—Formation of liver abscess.  
Complete microscopic section of right  
lobe of liver showing two amœbic  
abscesses. Numerous *E. histolytica*  
are visible microscopically within the  
marked circle.  
( $\frac{1}{4}$  nat size)



P H M F

*coli*, *B. enteritidis* (see p 223) or streptococcus and in these cases its character changes and it becomes green. At any time a liver abscess may become arrested and encapsuled. The pus is then partially absorbed and resembles thick cream cheese. Ultimately it may become calcified, the walls under these circumstances are often smooth and fibrous. On the other hand complete absorption may take place and A S Frv (1924) mentions two cases of large hepatic abscesses in which the cavities were obliterated leaving a cicatrix.

In long standing abscess pus, the causative amœbæ eventually die out altogether. Amœbæ are usually difficult to find when the abscess is first opened but when the cavity has been exposed to the air, they

appear. It was suggested by W. E. MacCallum (1937) that their need for oxygen influenced this behaviour.

When large or near the surface an amoebic abscess may cause a visible protrusion but more frequently it lies deeply and can be seen only on incision. This is specially noticeable when multiple abscesses are present. The liver is generally enlarged and fatty degeneration and venous congestion may be present but wherever the abscess is in contact with the peritoneum there is a localized peritonitis and adhesion of the liver to the dome of the diaphragm. According to Z. Cope (1920) the marked enlargement occasionally seen with a comparatively small abscess is due to great exudation of serous fluid. *Thrombosis of radicles of the portal vein may ensue.*

Old abscess cavities are enclosed in a wall of connective tissue internally the abscess wall is covered with necrotic tissue causing a peculiar shaggy appearance.

**Histopathology**—In the early stages the necrotic debris constitutes an area of cytolysed tissue cells in which red blood corpuscles degenerated liver cells a few leucocytes and connective tissue cells may be seen. In older abscesses the ill defined wall consists of connective tissue and the cavity is filled with necrotic liver cells and cytolysed granular material cholesterol Charcot Leyden and hematoidin crystals and fat globules. amoebae can be demonstrated in the walls and lodged between the less damaged liver cells. (Fig 26.) New bile channels are formed. On the whole association with cirrhotic changes in the liver is uncommon.

J. Hirtzmann (1922) has described engorgement of the capillary vessels with chains of amoebae and surrounding aggregations of eosinophil cells.

#### THE BILATERALITY OF THE LIVER

Until quite recently it has never been stated in any textbook that there is any difference in size between the right and left branches of the portal vein the right and left branches of the hepatic artery or the right and left hepatic ducts although the right lobe of the liver being treble the size of the left, it seems an anomaly that both lobes should possess vessels and ducts of the same size.

J. Cantlie in 1884 first noticed hypertrophy of the left lobe of the liver consequent upon total destruction of the right in a Chinese prisoner. At the post mortem the right lobe of the liver was found to have been completely destroyed by an old liver abscess leading to compensatory hypertrophy of the left.

In its embryological development the liver is at first an exactly symmetrical organ. It is only towards the end of foetal life that one lobe becomes larger than the other but that there should be a large right and a small left lobe is out of harmony with development and growth of any other organ. Cantlie was of the opinion that the existing anatomical division of the liver was incorrect and that its symmetry should be gauged not by the antero posterior or longitudinal fissures but by a line drawn from before backwards through the fundus of the gall bladder to the spot where the inferior vena cava grooves

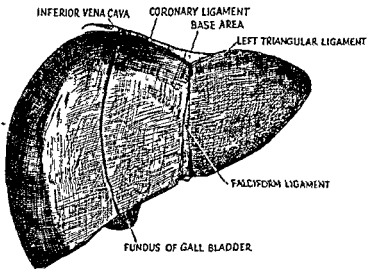


Fig. 27.—Superior surface of liver to show surface markings of the plane division.

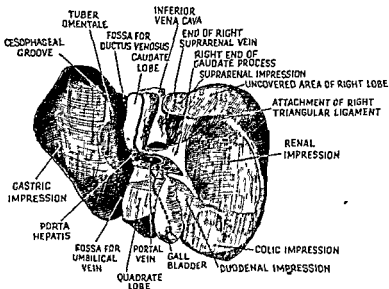


Fig. 28.—Inferior surface of the liver, showing the line bounding the plane of separation of the right and left lobes.



the back of the liver, this, then may be termed the nod line of the liver. Cantlie's view was borne out by pathological studies and also by the investigations of A. H. McIndoe and V. S. Counseller, who injected the portal vein, hepatic vein and hepatic artery with celloidin. They were thus able to show that the right and left branches of the portal vein are regularly and definitely divided in the manner that Cantlie had postulated and further that except for the intercellular sinusoids which are probably insufficient to maintain a collateral circulation there is no major anastomosis across the line of separation. Similarly, the right and left branches of the hepatic artery are separated in the same manner and at the same situation and the line of separation between the right and left hepatic ducts is identical with that of the artery and of the vein but the division is absolute (Figs 27-28). W. Seregé (1902) by injecting Indian ink into the mesenteric and splenic vein of the dog found in the former the ink distributed to the right lobe only whilst in the latter it was confined to the left. That these two distinct streams exist was confirmed by G. C. Copher and B. M. Dick (1928).

Therefore the embryological anatomical and pathological facts bear out the assumption that the two areas of the liver determined by this division

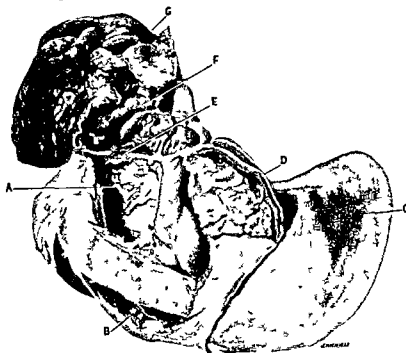


Fig. 29—Amœbic liver abscess showing hypertrophy of left lobe

The right lobe is partially destroyed by a large rugged abscess containing a plat of pus infected with streptococci. There are two smaller abscesses partially healed. There was also a sub-diaphragmatic abscess involving the right posterior subphrenic space. A large abscess cavity in right lobe. B smaller liver abscess which have not yet broken down. C hypertrophied left lobe. D falciform ligament. E aperture in diaphragm. F second right lung abscess. G lower lobe of right lung.

represent the true embryological right and left hepatic lobes, and that the falciform ligament, hitherto adopted as a division between the right and left lobes of the liver, is merely an arbitrary landmark.

The experience of recent years has verified the premises. The author's case, shown in Fig. 29, is another instance of the destruction of the right lobe by a large liver abscess, combined with hypertrophy of the left lobe. In this instance the hypertrophy apparently took about four months to become appreciable. Following three or more operations upon the abscess in the right lobe of the liver, a palpable tumour became noticeable in the left hypochondrium. It was at first thought to be the spleen, but later was recognized as a large left lobe. Similar instances have been reported, in which the right lobe has been destroyed through suppuration of the gall bladder owing to gall stones or to congenital stenosis of the common bile duct.

This theory has been criticized on the grounds that secondary carcinomata occur anywhere in the liver. J. W. McNee, however, points out that such secondaries are spread by the lymphatics, which do not divide as do the portal vein and bile ducts.

#### SYMPTOMATOLOGY OF HEPATIC ABSCESS

This is a particularly difficult subject to describe adequately, for in no other pathological condition possessing such characteristic features are the symptoms so variable. They may be obvious, or so obscure that clinical skill fails to elicit anything. Most physicians with a long experience of tropical practice can call to mind large abscesses which had destroyed the greater part of the liver without producing the generally recognized clinical picture.

As a rule, the patient is one who has long resided in the tropics and may at some time or other have suffered from amœbic diarrhœa or subacute attacks of dysentery. He becomes conscious, at first, of an uneasy sensation over the liver and in the right hypochondrium, and later begins to suffer from sharp stabbing pain in the hepatic area, accompanied by a dry cough. In a certain number there is also a sensation of rheumatic like pain radiating around the right shoulder joint, especially during the night. It may extend downwards as far as the angle of the scapula, and the skin over the acromial area is tender to the touch. This pain is now recognized as reflex and due to irritation of the phrenic nerve by stretching of the diaphragm, transmitted through the third and fourth and sometimes the fifth cervical nerves, to the supra acromial and supra clavicular cutaneous branches. So characteristic is this pain that, in abscesses of the left lobe of the liver, it may be referred to the left shoulder joint. In 800 fatal cases described by E. J. Waring (1854), pain in the shoulder region was recorded in forty eight.

Soon, other symptoms become apparent: the patient becomes feversish, particularly towards night time, and may experience a few short rigors. Accentuated rigors, such as have been described in amœbic hepatitis, are, however, rarely seen. The tongue becomes furred, the appetite is lost and the patient soon begins to lose weight. His complexion assumes a curious yellow subicteric tinge, in fact, what

January, 1928

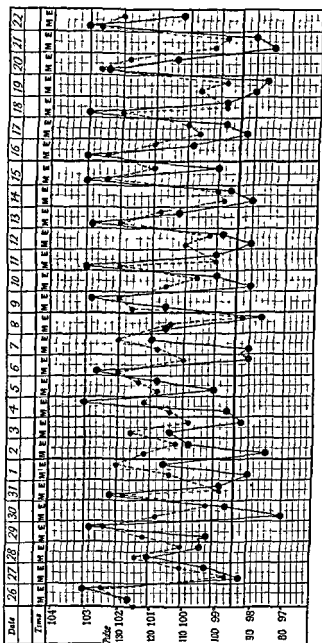


Chart 4—Fatal case of amoebic abscess of liver, showing tertian type of pyrexia. The dotted line indicates the pulse-rate.

is generally described as a muddy look. The quotidian rise of temperature now becomes a regular feature of the illness and the thermometer towards 10 p.m. may reach  $102^{\circ}$  F. even  $104^{\circ}$  F. sinking to normal or subnormal during the morning. These pyrexial bouts are accompanied by profuse sweats which necessitate a frequent change of clothing during the night. Insomnia or restlessness at night is usual. Occasionally a tertian type of temperature is encountered (Chart 4).

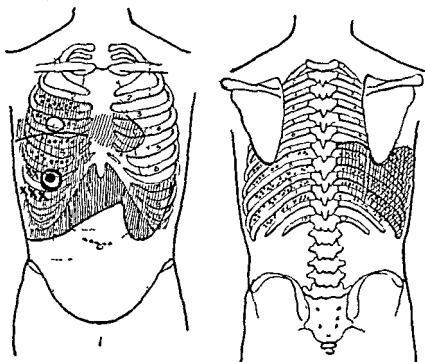


Fig. 30—Liver abscess with rupture through the diaphragm secondary pulmonary abscess and compensatory hypertrophy of left lobe of liver

Dilated stomach, considerable secondary anaemia and *F. & stolon* cysts in faeces. Note physical signs at base of both lungs. Death from streptococcal septicaemia. Indian infection of 11 years latency. (●) site of abscess. XXX pleural rub

During the daytime the patient's extremities are cold and clammy, and his breath is shallow and mainly thoracic. On inspection a fullness of the epigastrium may sometimes be observed or there may be an acute bulging over the hepatic area. Occasionally too as Manson originally pointed out there is dysphagia or pain on swallowing which is referred to a point mid way on the sternum. In the majority of cases a deep seated pain is produced by palpation and heavy percussion over the hepatic area, where the lower border of the liver is found to be jutting below the costal margin. An especially tender spot is to be

found over the right rectus muscle in the gall bladder area, which is deceptive as it may lead to a diagnosis of cholecystitis.

Less frequently the liver dullness extends an inch or more above normal level in the nipple line and, on percussion, it can be observed that the line of dullness is altered by changes in position, when the patient lies on his left side, or stands up. Attention must be drawn to the flatness of this note, which differs in tone from that of chronic venous congestion or other conditions. Deep inspiration may give rise to acute pain, and sometimes one or two especially tender spots may be discovered in the lower intercostal spaces. Unless the disease is complicated by malaria, the spleen is not enlarged, but, as pointed out on p. 210, a tumour in the left hypochondrium, which is separated by a resonant zone from the left lateral margin, may be due either to an independent abscess of the left lobe of the liver or to compensatory hypertrophy (Fig. 30).

On auscultation a pleuritic rub may be detected at the base of the right lung and over the whole of the hepatic area or there may be extensive signs of compression of the base of the right lung. Sometimes

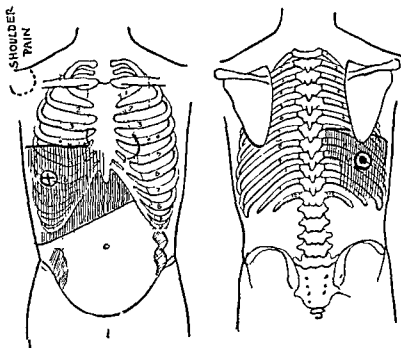


Fig. 31—Liver abscess, Indian infection with shoulder pain, no *E. histolytica* cysts in faeces; leucocytes, 22,000

Three preliminary aspirations. No reaction to emetine. Open operation. ⊕ point of maximum tenderness. ⊙ site of abscess.

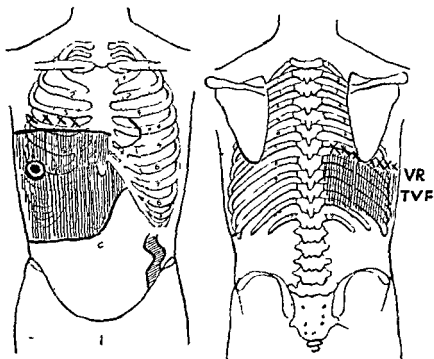


Fig 32.—Liver abscess, Indian infection, with *E histolytica* cysts in fæces, leucocytes, 18 000

Preliminary aspiration, 30 fl oz subsequently open operat on Carrel Dakin drainage  
 XXX friction rub VR vocal resonance diminished TVF tactile vocal fremitus diminished, ⊙, site of abscess.

an effusion of fluid into the pleura may be present which is as a general rule, serous in character. It may be abundant, and on aspiration may prove to be genuine liver abscess pus and may contain active *E histolytica*. It will thus be realized that to the tropical physician signs at the base of the right lung assume exceptional importance for they indicate some underlying disease of the liver (Figs. 31-33). "Litten's diaphragm sign, the indrawing of the lower intercostal spaces during normal inspiration, with the patient lying prone and the head slightly elevated, may be observed. Alterations in the level of the shadow cast by the intercostal spaces indicate some interference with the normal movements of the diaphragm or a morbid condition of the corresponding lung or pleural cavity.

In less extensive cases, a decrease in the breath sounds, a few inspiratory crepitations, or a diminution of the vocal fremitus may be noted. Pain is usually relieved by lying upon the affected side.

As the case progresses so the patient becomes more and more emaciated, and the fever with nocturnal sweats increases. On the whole, general enlargement of the liver becomes more obvious and percussion

may now disclose a tender area or local œdema of the chest wall which indicates the direction at which the abscess is pointing. Unless relieved by operation the patient dies worn out by emaciation after months of prolonged misery or the abscess which by now may have attained a great size may burst into the right lung, the pleura or the internal viscera and be discharged. This too may cause the death of the patient but sometimes brings about ultimate recovery—Nature's somewhat crude method of effecting a cure.

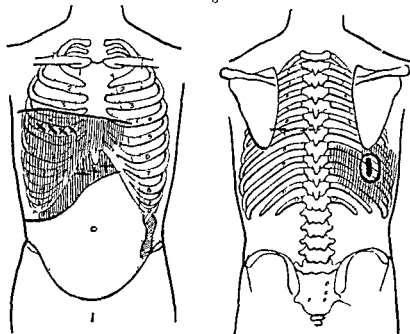


Fig. 33—Liver abscess Iraq infection with active *E. histolytica* in faeces leucocytes 23 000 and pleural effusion at base of right lung. Latent period 12 years.

Open operation + Currel Dakin irrigation + E.R.L. med. c. on. XXX f. let. on rub.

○ = c. of abscess.

Although the foregoing account can be taken as describing the average case of hepatic abscess there are many in which the initial symptoms are much more urgent and the disease progresses more rapidly. In other rare instances the symptoms may be entirely absent and the case non febrile so that until the abscess bursts or until a post mortem examination reveals its presence the possibility of a liver abscess may not have presented itself. Sometimes the initial fever is so high and so strikingly remittent in character that it may be mistaken for that of some febrile illness such as typhoid but later it usually becomes distinctly quotidian or intermittent.

Enlarged cervical and axillary glands may sometimes be observed on the affected side, while the rheumatic like pain and swellings, which are apt to accompany any chronic infection may cause difficulties in diagnosis

In large abscesses, a sense of fullness or weight in the region of the liver is complained of, and a stabbing and stitch like pain. The patient endeavours, as Koch so pithily expressed it, "to carry his liver like a football under his arm". At all events, that is the sensation he often describes, and he may walk with the shoulder on the affected side depressed. The heart may be displaced laterally or upwards by pressure and show tachycardia and irregularities.

Swellings of the epigastrium or hypogastrium, closely simulating abdominal tumours, and varicosity of the epigastric veins may also be observed. Signs of previous dysenteric infection in the abdomen may be apparent, such as infiltration and thickening of the cæcum or sigmoid colon, and cysts of *E. histolytica* may, or may not, be discovered in the fæces.

In order to appreciate the frequency of particular symptoms in hepatic abscess, the following tables have been constructed from a series of the author's cases over a period of ten years —

## TABLE XII

## Total Number of Liver Abscess Cases, 45

Ages, 16-63

Sex males, 39, females, 6

Deaths, 3 (6 per cent) one from toxæmia, one from septicæmia, one from pneumothorax

Abscess in right lobe, 40

Abscess in left lobe, 5 (two being in women)

History of previous dysentery, 27 (60 per cent)

*Entamoeba histolytica* or cysts present, 21 (45 per cent)

Shoulder pain right, 20 (44 per cent), left 2 (4 per cent)

## Pyrexia —

Intermittent typical fever, 35 (77 per cent)

Remittent typhoid like fever, 4 (8 per cent)

Sudden onset with rigors 2 (4 per cent)

Absent, 6 (13 per cent)

Night sweats, 37 (82 per cent)

Dysenteric thickening of the bowel —

Sigmoid flexure, 12 (24 per cent)

Cæcum as well as sigmoid, 4 (8 per cent)

Enlargement of the liver —

In upward direction, 11 (24 per cent)

In downward direction 34 (75 per cent)

Tenderness and pain in liver, 26 (57 per cent)

Displacement of heart by abscess —

Outwards, 4 (8 per cent)

Upwards and outwards, 1 (2 per cent)



Obvious swelling of chest wall, 3 (6 per cent)  
 Enlarged and tender lower cervical glands, 2 (4 per cent)  
 Enlarged and prominent epigastric veins 3 (6 per cent)  
 Associated signs at base of right lung, 31 (75 per cent)  
 Pleurisy and pleuritic rub, 6 (12 per cent)  
 Associated signs at base of left lung, 2 (4 per cent)  
 Rupture of abscess into lung 5 (11 per cent)  
 Leucocytosis 8 500-35 000, 40 (88 per cent) (mean, 16,000)  
 No leucocytosis, 5 (12 per cent) Mean differential count  
     polymorphonuclears, 70.8 per cent, lymphocytes, 22.2 per cent,  
     large mononuclears, 6 per cent, eosinophils, 1 per cent  
 Grave anaemia, 8 (17 per cent) Most severe anaemia noted RBC  
 1,375 000, haemoglobin, 40 per cent (See p 232)

There are no records of liver abscess in a person who has been resident in the tropics under one year usually the length of residence varies from two to three years In the series cited above, a recent history of diarrhoea or dysentery was obtainable in just 60 per cent of the cases, while cysts of *E. histolytica* were present in 45 per cent, in only two cases were entamoebae present in the faeces together with active dysenteric symptoms

It is a curious observation to which J. Twining as long ago as 1852, drew attention that, so soon as a liver abscess becomes established, any dysenteric intestinal symptoms which were previously apparent, subside

In this series, too, the abscesses were solitary, except in one very rapidly fatal case, in which they were multiple In the majority of the forty five cases the abscess was situated in the upper and posterior part of the right lobe of the liver, and in five it was situated in the left lobe

Usually the accompanying fever was of a hectic, frankly remittent character with nocturnal excursions in two cases the fever was so high and remittent that typhoid was at first suspected

It is not generally realized that afebrile cases of liver abscess, often with large accumulations of pus, may be encountered, usually in these cases there is no accompanying leucocytosis, so that the diagnosis may not be beyond question until after the operation This has also been noted by A. G. Biggam and P. Ghahoungui in 1933 in Cairo

An ex officer was seen in 1921 after service in East Africa On account of his extreme emaciation and anaemia and also on account of the chronic dyspepsia from which he had suffered and which was accompanied by a large palpable mass in the left hypochondrium he was regarded as a case of malignant disease The temperature chart showed that he had never suffered from fever, while the leucocyte count was 7,000 c mm Aspirations from the eighth right intercostal space yielded 64 ounces of typical liver abscess pus After adequate treatment he made a complete recovery and entirely regained the weight he had lost

There may be nothing in the patient's appearance to suggest a liver abscess, for the facies may show no sign of the condition, which may

be unaccompanied by digestive disturbances and may, in fact, co exist with a state of good health.

In 1927 a man aged sixty five, apparently in good health, who had returned to England from Hongkong two years previously, while playing a game of golf, suddenly coughed up a large amount of liver pus, and nearly died from the resulting dyspnoea. It appeared that a liver abscess had burst into his right bronchus the only premonitory symptom being a bout of uncontrollable hiccough. He made a good recovery and no other signs of liver abscess developed.

A second instance occurred in a girl of sixteen who was seen in 1928. She had never suffered from any localizing symptoms, but suddenly a swelling appeared in the right hypochondrium. It proved to be an abscess of the right lobe of the liver which was tracking along the falciform ligament without causing any apparent disturbance of health. The abscess was opened and drained and the patient made a good recovery. It appeared on questioning that she had suffered from some form of dysentery in Cairo when about three years of age.

*Night sweats* —Night sweats were a prominent feature of 82 per cent of the series tabulated, and involved the whole of the body.

*Enlargement of the liver* —In the majority of cases the enlargement of the liver takes place downwards into the abdominal cavity, this occurred in 75 per cent of the series, in only 24 per cent was it enlarged upwards towards the nipple line.

Although there is usually considerable enlargement of the liver, yet there may be none. In the author's series a large abscess has been found to contain two pints of pus or more in a case in which an X ray film and screening of the diaphragm had shown nothing abnormal.

*Jaundice* is infrequent in an uncomplicated liver abscess but may occur through pressure on the hepatic ducts, according to Z. Cope. Bile in the discharge from a liver abscess sinus may be due to rupture into the common bile duct.

*Rupture* —An amœbic abscess may rupture into almost any contiguous organ, and thereby a spontaneous cure may be produced (Fig. 34). Usually it bursts into lung or pleura. When it ruptures into the lung, the contents are suddenly coughed up as dark pus mixed with blood, so that the patient may be almost suffocated. On the other hand, rupture may not occur so suddenly, in this case the expectoration is less, a few drachms being brought up at a time, and induces a chronic condition resembling bronchiectasis, indeed it is quite common for amœbic abscess of the lung resulting in transdiaphragmatic rupture to be mistaken for pulmonary tuberculosis. Unfortunately, in these cases the amœbæ are not usually present in the sputum. Many years ago Manson pointed out that rupture through the diaphragm resulted in a valve like aperture, so that the abscess cavity in the liver could discharge only when full. Arrest of discharge from the lungs may not mean recovery, and cessation of cough may be followed by pyrexia and the re appearance of night sweats, so that alternate emptying and refilling of the abscess cavity may recur many times before the patient finally recovers. In some cases the

abscess becomes chronic and is accompanied by other signs of pulmonary absorption such as respiratory distress and clubbed fingers. Sudden rupture may result in the swallowing of much blood and consequent melæna.

Rupture into the pleura is by no means as common as rupture into the lung. It may lead to a suddenly developed pleural effusion and the signs of empyema and in one particular instance the author was able to demonstrate amœbæ. A distinctive character of the cellular

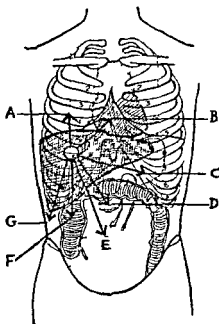


Fig. 34.—Diagram to show possible directions in which a liver abscess may burst.

A lung B pericardium C, stomach D duodenum E peritoneal cavity  
F caecum G peritoneal fat

picture may be the high proportion of eosinophil cells as described by V. Corder and L. Morenas (1930).

Rupture may take place into the stomach causing vomiting of pus, or into the bowel causing diarrhoea and discharge of the pus with the faeces or the abscess may burst with immediately fatal results into the pericardium or peritoneum. Choledocal fistula (rupture into common bile duct) has been recorded by J. M. Berkman and J. A. Bergen. Rupture into the inferior vena cava may occur rarely. Finally the abscess may rupture through the skin of the abdominal wall and evacuate itself painlessly. This is the most fortunate and natural termination. The skin around such a spontaneous rupture

may, however, become secondarily infected with amœbæ, with resulting ulceration

Chronic suppuration from a liver abscess may lead to amyloid disease, a rare complication which is seldom encountered in modern practice, as in the case recorded below —

The patient had spent most of his life in the Transvaal, and his illness was of some seven years' standing. It began with what was considered to be a right sided pleurisy, which necessitated rib resection and residence of five months in hospital. In 1930, amœbic dysentery declared itself and a liver abscess was suspected, two years later a large collection of pus was noted in the left pleura, and eventually thoracoplasty had to be performed, the pus which was evacuated was of "anchovy sauce" character. For the first time emetine was exhibited, with excellent results.

Edema of the face and legs soon after became apparent, and on his admission to hospital in 1932, nephrosis was obvious. The urine contained 10 grammes per 100 c.c. of albumin (Esbach) and numerous granular and hyaline casts. Small healed amœbic ulcers were demonstrated by sigmoidoscopy, but no other evidence of active amœbiasis was obtained. The patient presented the waxen, yellow faces of amyloid disease, and a grave prognosis was given.

**Mortality.**—In the early years of last century the case mortality from liver abscess was very high—something like 50–80 per cent—specially in the British Army. Owing to advances in diagnosis and treatment however, the death rate has since fallen very considerably, so that deaths from liver abscess are extremely rare at the present day. When death ensues it may be due to pressure of the abscess itself, to secondary infection by streptococci or *Bacillus coli*, to gangrene of the abscess wall, to pneumothorax, to anæmia, or to some intercurrent disease. In the author's series of forty five cases there were three deaths, one being due to pneumothorax, and two to septic infection of the abscess cavity. The mortality rate was 6 per cent, and this probably represents the average death rate at the present day.

### DIAGNOSIS

There are few serious tropical diseases so frequently overlooked as liver abscess, this is due to the variety of symptoms. As a French surgeon has put it, "it is easier to operate upon a liver abscess than to diagnose it." The diagnosis is more easily arrived at in the acute than in the chronic cases.

The following are mistakes commonly made in diagnosis —

- (1) Failure to recognize the presence of any disease,
- (2) Misinterpretation of the signs at the base of the right lung. Their true significance may not be appreciated, and a primary lung disease may be diagnosed,
- (3) Attribution of the associated fever to malaria, syphilis, or other febrile process,
- (4) Mistaking other diseases, such as non suppurative hepatitis or the hepatitis found in association with malaria, etc. for abscess of the liver.

**Differential diagnosis**—The differential diagnosis of liver abscess, considered *in extenso* is a large subject, and presents many practical difficulties. Differentiation has to be made from all the other febrile conditions it may simulate from the continued fevers such as typhoid, undulant fever, and tuberculosis and from intermittent fevers such as malaria. Indeed, Manson remarked that he had never encountered a liver abscess in European practice which had not previously been saturated with quinine and that it should be considered a golden

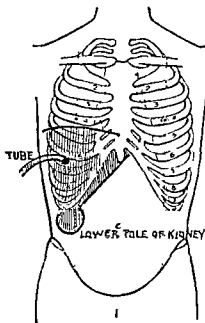


Fig. 35.—Perinephric abscess regarded as liver abscess. Diagnosed by cystoscopy and lipiodol injection and opened through diaphragm.

Calculus in right ureter streptococci in urine leucocytes, 120,000

rule to suspect hepatic abscess in all cases of abdominal disease associated with an evening rise of temperature.

In a case from the tropics presenting rigors and sweats the following have to be considered in making a differential diagnosis: malaria in which the sweats occur after the rigor; kala azar with night sweats and less persistent rigors; undulant fever rarely associated with rigors but with continued sweating.

Then it must be differentiated from all other diseases involving the liver, a matter often of difficulty from gumma, tuberculous abscess (Huard and Meyer May), malignant disease, suppurating hydatid cyst (Gaide, 1918), pyæmic abscess due to gall stones, empyema of the

gall bladder, suppurative cholangitis and ascending pyelephlebitis, and, it may be from *Bilharzia* infections. The differential diagnosis of lung complications—unresolved pneumonitis, pleurisy, pleuritic effusions, empyema, tuberculosis—must be considered. Finally, there is the differential diagnosis from perinephric abscess and pyonephrosis. The author has encountered two cases of perinephric abscess which had been mistaken for abscess of the liver, in one drainage through the liver had actually been instituted, and the true nature of the disease remained unrecognized till revealed by radiography (Fig 35). An important point is the differential diagnosis from subphrenic abscess (see p 229). Carcinomata of the liver may simulate abscess so closely and may give rise to such hepatic and pulmonary signs as almost to defy differential diagnosis, save by laparotomy.

Liver abscess may occur in association with *Ascaris lumbricoides*, through migration of this parasite into the common bile duct (Girges), it has been reported, too, in the glanders like disease melioidosis (Stanton and Fletcher).

The occasional passage of blood in liver abscess may simulate that of duodenal ulcer, and the clinician should bear in mind that occasionally metastatic abscesses occur in association with duodenal lesions as well as with diverticulitis.

### Case illustrating peculiar difficulties in diagnosis

In 1938 the patient had been invalided from India with a continued pyrexia which had lasted for three months. At first a typhoid infection had been suspected and a positive agglutination of the serum to O antigen in a dilution of 1:1,200 was obtained, but this was soon found to be fortuitous and to be the expression of co agglutination to *B. enteritidis*, and the same serum reacted to this organism in 1:6,400. Further proof was forthcoming when this bacillus was isolated from the faeces. The physical signs in liver and abdomen—the shoulder pain and pressure signs at the base of the right lung—were those of liver abscess, which was confirmed by X-ray examination, which showed restricted movement of the right diaphragm and a circular less opaque area in the liver substance, but there was no leucocytosis—the count being 6,400 with a polymorphonuclear percentage of 63. The diagnosis of liver abscess was confirmed by aspiration of 600 c.c. of typical pus in the seventh intercostal space and from this a pure culture of *B. enteritidis* was obtained. The explanation appears to have been a hepatic abscess in a carrier of this organism, so that the infection became centred in the liver abscess pus as a 'fixation abscess'.

### Cases illustrating points of differential diagnosis

*From ascending pyelephlebitis*—A man of thirty-two was seen in hospital in February, 1925 on his return from Central Africa where he had spent nine years. For one month he had been complaining of pains and occasional vomiting, accompanied by pyrexia and rigors uncontrolled by quinine. On examination attention was directed to the liver, which was enlarged, with local oedema and tenderness in the right mid axillary line. The abdomen

was protuberant, sclerotics and skin were slightly icteric, and there were definite signs of anaemia. There was a leucocytosis of 20,000 (Chart 5).

The supposition of hepatic suppuration with biliary involvement was supported by a positive direct and indirect Van den Bergh reaction (8 units). The urine contained traces of bile and excess of urobilin. An X ray examination disclosed doming and bulging of the diaphragm, as in liver abscess, with definite fixation.

So far, the signs and symptoms pointed to abscess formation within the

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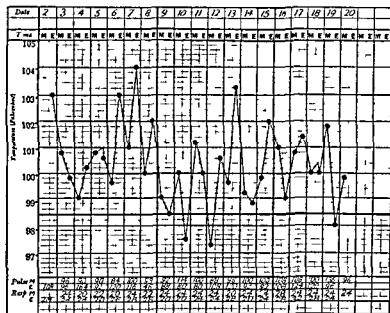


Chart 5.—Ascending pyelophlebitis secondary to an appendix abscess, simulating amœbic abscess of liver.

liver, but the presence of icterus could be taken as against the amœbic origin of the disease.

The probability of extensive intra abdominal suppuration received support from the frequent rigors and the somewhat irregular nature of the temperature chart. Unfortunately, after an exploratory aspiration of the liver in which bile stained pus was obtained, the patient suddenly died. At the autopsy numerous small metastatic abscesses of the liver were found, which had originated from an old and partially encysted retroperitoneal appendix abscess.

*From suppurative cholangitis*—A man of forty three was admitted to hospital in September, 1930. He had served in India during the War, 1917-20, and had suffered from amœbic dysentery. Small wonder then that when he began to complain of pain in the liver with rigors, the possibility of liver abscess was considered. The liver was found to be much enlarged and

tender, and there were associated signs at the base of the right lung. The signs and symptoms, supported by radiography, pointed to an abscess in the upper part of the right lobe. There was a leucocytosis of 18,000 with 80 per cent polymorphs. A large right sided pleural effusion was aspirated and proved sterile, but blood stained pus was obtained from the underlying hepatic abscess which produced on culture an abundant growth of streptococci. The patient eventually died, after a month in hospital, and, at autopsy, suppurative cholangitis with numerous secondary pyæmic abscesses in the liver proved the correct diagnosis. (Chart 6.)

*From malignant disease of the liver*—A retired regular soldier, aged fifty six  
September 1930

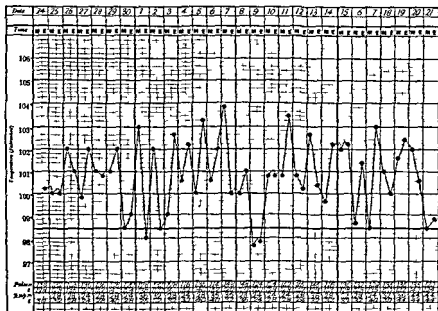


Chart 6.—Suppurative cholangitis due to gall-stones simulating amœbic abscess of liver.

years, was seen in March, 1936. After a residence in India of twenty years he had been in the south of England for two years. He gave a history of illness of one year's duration commencing with an irritative cough followed by definite shoulder pains. Wasting, accompanied by night sweats, gradually occurred, associated with definite liver pain, and for the last two months an intermittent pyrexia had been noted. (Chart 7.)

No suggestion of the malignant character of the illness was apparent externally, and, when first seen, the case certainly resembled liver abscess. It is true that there was no previous history of dysentery, but the physical signs, shown in the diagram (Fig. 36) were compatible with those of amœbic abscess, there was an intermittent pyrexia (99°–100° F), and a leucocytosis of 22,000. In the differential leucocyte count the polymorphonuclears were rather high (91 per cent). The X-ray appearances were suggestive of a liver abscess, and to complete the story *E. histolytica* cysts were found in the stool.



One disquieting feature was the appearance of a trace of bile and an excess of urobilin in the urine, but the Van den Bergh reaction was within normal limits

Operation was advised, and disclosed a small primary carcinoma of the stomach, with numerous secondary nodules in the liver

*From cholecystitis, empyema of gall bladder, gumma, and hydatid cyst —* The differential diagnosis from empyema of the gall bladder, or even from cholecystitis may give rise to difficulty, especially when the abscess is situated as it so often is in the anterior portion of the right lobe

*Amoebic abscess of liver (left lobe) simulating acute cholecystitis —*

March 1930

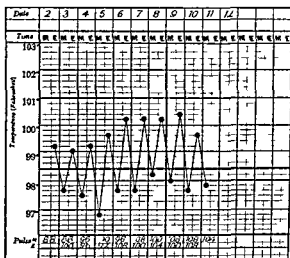


Chart 7 — Carcinoma of liver with pyrexia simulating amoebic abscess.

W I C 35 examined in June 1939 from Sudan. Previous history attacks of malaria at intervals typhoid 1927 paratyphoid 1930. Recent recurrent attacks of fever (T 102° F) with severe subcostal pain. No history of dysentery. No *I. histolytica* cysts or free forms in faeces. Leucocytosis 21,000 (Polymorphs 79 per cent). Rigidity of right rectus muscle. Pain on pressure over gall bladder area. Cholecystogram showed dilated distended gall bladder. No alteration of diaphragm seen by X-ray. Operation June 29 1939. Amoebic abscess left lobe pointing to mid abdominal line. Aspiration—Potain's aspirator—10 ozs typical liver pus evacuated. Subsequent combined course of EBI and quinoxyl. Uneventful recovery.

In differentiation the therapeutic action of emetine is often of diagnostic value in that should inflammation be of amoebic origin,

the response is almost immediate. The character of the temperature chart, the frequent rigors, the persistence of urobilin in the urine, a high Van den Bergh reading, and the leucocytosis with a relatively high polymorphonuclear count, are all points which will assist Murphy's sign—hyperæsthesia over the gall bladder area—is a most important physical point in differential diagnosis.

*Paralysis of right dome of diaphragm*—A case presenting particular difficulties in diagnosis by reason of the X ray appearances was seen in a Norwegian

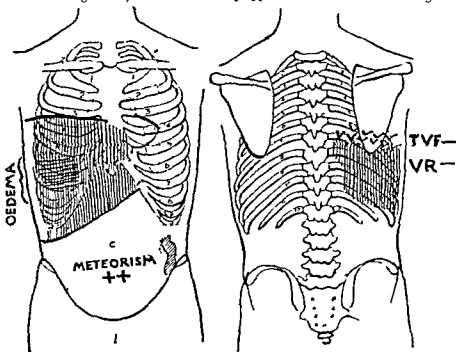


Fig 36—Carcinoma of liver primarily diagnosed as amoebic abscess.

Loss of 35 lb in weight slight oedema of legs VVV apophony TVF tactile vocal from tug, diminished VR vocal resonance diminished

ship's engineer in 1941. There was great enlargement of the liver with doming and complete immobility of the right cupola of the diaphragm with a leucocytosis of 11 000 and associated signs at the base of the right lung. An exploratory laparotomy revealed no abscess while at autopsy multilobular cirrhosis of the liver with collapse of the lower lobe of the right lung declared itself.

From a suppurating gumma of the liver distinction may also have to be made. This does not often arise—some three times in the author's experience. Usually there are other stigmata of syphilis to be noted and the Wassermann reaction is positive.

Suppurating hydatid cyst presents another difficulty which can be solved only at operation. Usually in this infection recurrent jaundice is a noticeable feature.

A case of this description was seen by the author together with Mr H E Griffiths in 1922. The prominent feature was the localized character of the abdominal swelling which caused a marked prominence in the epigastrium. The suggestion of hydatid cyst was supported by the association of the patient with dogs and the eating of watercress.

The associated symptoms are by no means so characteristic, and as aids to diagnosis the eosinophilia which accompanies hydatid infection

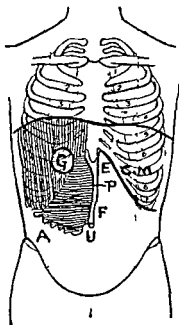


Fig 37 —Abdominal signs in anterior (gastric or duodenal) variety of right anterior intraperitoneal subphrenic abscess

P falseform ligament bulging to left. A band of adhesions from umbilicus to costal margin. P pus in contact with abdominal wall. G gas-bubble over liver dullness. U umbilicus. E, ensiform. C.M. costal margin.

and the intradermal Casoni test (which is valuable) must be taken into account.

*From non parasitic cysts of the liver* —R Maingot (1940) has described these as single or multiple more common in females than males. They may occur at any age mostly in children. The following classification is suggested —blood degeneration cysts, dermoid, lymphatic or endothelial cysts, cystic adenomata or those due to biliary obstruction. Multiple cysts may be limited to the liver but most commonly are associated with cysts of kidneys, pancreas or other organs or polycystic disease. Solitary non parasitic cysts of the liver are congenital, of biliary origin, perhaps arising from aberrant bile ducts resulting in

benign cystic adenomata These cysts are usually situated in the right lobe of the liver

*Differential diagnosis from subphrenic abscess*—Subphrenic abscess is less commonly seen at the present time than formerly The usual cause is perforation of a gastric or duodenal ulcer, out of seventy six cases recorded by H L Barnard (1910), it was due to perforation in twenty six, the ulcer being gastric in twenty one and duodenal in five The left anterior intraperitoneal fossa was usually affected This fossa is bounded above by the diaphragm to the right by the left lobe of the liver, and to the left by the spleen, and by adhesions of the omentum to the abdominal wall (Fig 87)

As in liver abscess, there are associated signs at the base of the lung but in these cases it is generally the left lung which is affected An abdominal swelling can usually be recognized, occupying a triangular area limited by the costal margin on the affected side and by a line which is convex to the right, joining the umbilicus to the ensiform, and the ensiform to the costal margin Gas is usually present, and this, as a rule, gives rise to resonance in the upper part of the swelling, this sign alone should be sufficient to distinguish doubtful cases from amoebic liver abscess This tympanitic note may be as high as the mid axillary line and may easily lead to a mistaken diagnosis of pneumothorax

When the perforation is at the pylorus, in the duodenum, or in the appendix, the right anterior intraperitoneal space may be affected Out of twenty seven abscesses of this type recorded by Barnard four were the result of a perforated gastric ulcer, and two were from perforation of a duodenal ulcer The fossa in these cases is situated behind the diaphragm above, the right lobe of the liver below, and the falciform ligament to the left As in liver abscess, there may be physical signs at the base of the right lung

The right posterior fossa (the subhepatic or right renal fossa) is seldom affected, of ten abscesses in this situation, one was due to a gastric and one to a duodenal ulcer Rarely, the abscesses involve the lesser sac of the peritoneum (the left posterior intraperitoneal situation of Barnard) Two cases of this kind, out of three, were due to a perforated gastric ulcer, but the lesser sac was not affected alone

These are the physical characteristics of subphrenic abscess It will be seen that the maximal signs and symptoms are situated below the diaphragm and that there is absence of those signs which indicate actual destruction of liver substance As in liver abscess, however, unless the condition is relieved, the pus may find its exit spontaneously, the abscess bursting into a bronchus, into the pleura, with the formation of a pyopneumothorax, or into the stomach or intestine It rarely ruptures through the skin

The onset of a subphrenic abscess may be acute and present most of the features associated with an intra abdominal condition, or it may be subacute, with pains in the upper part of the abdomen, fever, and

possibly a rigor. Pains in the shoulder are common. Pain and tenderness over the lower ribs with limitation of the respiratory movements are usually present, together with a cough, slight expectoration, and irregular fever.

Inquiry in a typical case will show that an accident followed upon a history of acute indigestion, an operation for suppurative appendicitis or other recognizable cause of subphrenic suppuration.

The physical signs, like the symptoms, are subject to wide variations. Signs of a limited collection of fluid at the base of the left lung are usually present. In a well marked case there is an area of dullness clearly marked off from the resonance of the lung above, together with loss of breath sounds and diminution of the vocal resonance. When the abscess contains much gas a remarkable series of notes up to a tympanic one may be obtained on percussion. In advanced cases the lower lobe of the lung may be so compressed as to give a zone of tubular breathing and impaired resonance extending above the level of absolute dullness. The diagnosis is often complicated by the presence of clear or purulent fluid in the pleural cavity above the subphrenic collection of pus. The diaphragm itself may be perforated so that the subphrenic and pleural abscesses connect with one another. Under these circumstances the mortality from subphrenic abscesses is 30-40 per cent.

Generally speaking, a liver abscess is associated with a marked dull note over all the liver area while the subphrenic has a resonant note of gas at one point at least.

Despite these symptoms and signs, it is notorious that the diagnosis of subphrenic abscess may present amazing difficulties as, indeed, Barnard's famous dictum, Pus somewhere, pus nowhere—pus under diaphragm, so freely admits. This subject has been specially studied by S. Wirssaladse (1937).

**Aids to diagnosis of hepatic abscess**—Actual dysenteric symptoms are very seldom present in association with liver abscess, but usually some evidence of previous ulceration of the large intestine may be obtained by palpation of the abdomen when infiltration of the sigmoid flexure (24 per cent. of cases) and of the cæcum (8 per cent.) may be elicited.

Sigmoidoscopic examination may assist (see p. 178) but it is not always possible to obtain evidence of ulceration of the lower bowel, as this is usually in and around the cæcum far beyond the range of the instrument.

**Examination of the fæces**—When there are clinical evidences of hepatic abscess, the discovery of *E. histolytica* cysts in the fæces is of great confirmatory importance.

**Blood-examination** *Leucocytosis*—In association with pus formation within the liver, it is reasonable to expect an increase of the leucocytes, and usually there is a genuine increase, it varied from

9,000-35,000 in 88 per cent of the author's series. It must be noted that, in contradistinction to pneumonia and other septic conditions, the total increase of the leucocytes is seldom very high. The average is about 15,000. An actual increase of polymorphonuclears above 80 per cent is rare, in the author's records this occurred only six times. The highest differential count recorded was 88 per cent and once there was a polymorphonuclear count as low as 35 per cent. As a general rule, the leucocytosis is higher with acute accumulations of pus, and lower with larger quantities. There may be, as in five cases

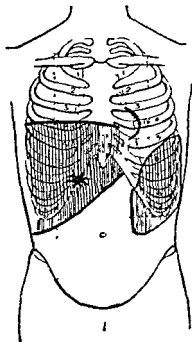


Fig. 33.—Liver abscess with splenomegaly (malarial) and advanced anaemia. Recovery on emetine treatment.

Hæmoglobin, 40 per cent, red cells, 1 375 000. Grave blood changes. Wassermann reaction ++. \* point of maximum tenderness.

of the author's series, no increase of the leucocytes—a fact which may lead to considerable difficulty in arriving at a correct diagnosis. The average differential leucocyte count in the author's series, in association with H. M. Willoughby (1929), was as follows: polymorphonuclears, 70 per cent, lymphocytes, 22 per cent, large mononuclears, 6 per cent, and eosinophils, 2 per cent. Occasionally, however, eosinophilia is encountered, and may be, as in one case, as high as 60 per cent. In these instances, some additional exciting cause may be present, for instance, asthma, so that the intrahepatic suppuration stimulated the already existing eosinophil response.

*Anæmia*—Anæmia is not a constant feature of liver abscess, unless absorption of septic material has proceeded for a considerable length of time. Grave anæmia with a reduction of the hæmoglobin below 80 per cent has been encountered in eight cases, but in only one has the author observed changes so extreme as to resemble a genuine pernicious anæmia.

A Goanese steward was seen in October 1928, with enlarged liver and spleen the result of old standing malaria. The hæmoglobin was reduced to 40 per cent and the red blood corpuscles numbered 1 375 000 with normoblasts and alteration in the size of the cells. Remarkable improvement of his blood picture took place after aspiration of the liver abscess and emetine treatment (Fig 38).

**Radiological evidence**—An X ray examination may be extraordinarily helpful or it may be the opposite. The salient points to observe are fixation and limited movement of the diaphragm on the affected side, and sometimes irregularity of its outline. The increase in the size of the liver, and especially the projection of the lower margin into the abdominal cavity, may also be visualized and can best be seen by screening.

In the author's series doming of the diaphragm on the right side afforded an efficient help in one third of the cases. The picture showed stretching of the diaphragm, sometimes  $2\frac{1}{2}$  to 3 inches beyond the normal limitation of movement, and indistinctness or blurring when a rupture into the pulmonary cavity was imminent (Plate X). In one instance the valve-like opening through the diaphragm into the pleural cavity was visualized. E Bressot (1930) says that the right cupola should surpass the left by 2 cm but in the case of a right lobe abscess it may surpass it by 6 or even 10 cm. Attention should be paid to alterations in the cardiophrenic angle which should the abscess be laterally situated becomes less acute more nearly approaching a right angle (Plate X), but if the abscess is nearer the vertebral column, the angle is more acute. Serous effusions into the pleural cavity and secondary abscesses in the lung may be seen but it is disappointing that the actual abscess cavity within the liver itself has not often\* been accurately demonstrated by radiographic means (Plate XI, left).

The value of thorium dioxide in the diagnosis of liver abscess has been emphasized by R T Reeves and E D Apple (1933). Thorium dioxide (thorotrast) is given intravenously in 12 c.c. doses with a total of 72 c.c. over a period of fourteen days. Three days after the last injection X ray examination disclosed an enlarged liver and the outline of the liver abscess. In three of the author's cases the cavities were partially calcified and their outline could be seen in the radiograph. After aspiration the cavity occasionally becomes filled with gas and may give a shadow marking the abscess site (Plate XIII p 426).

P Heymann (1923) has recorded ten cases in which pneumoperi-

\* The author recently treated a case in which a less opaque area in the liver substance delimited the actual cavity and formed an accurate guide to aspiration.

toneum has been used with success in locating abscesses of the liver. By this method the organ is surrounded by a gaseous zone which renders its outline visible.

Radiography assists in the differentiation of liver abscess from subphrenic abscess, tuberculosis of the lung, and empyema.

**Aspiration as an aid to diagnosis**—The most practical method of demonstrating the presence of an abscess is by aspiration—by drawing up liver pus into the exploring syringe. Anatomical details have to be borne in mind by the operator. At no point should the aspirating needle be inserted for a distance greater than  $3\frac{1}{2}$  inches from the chest wall. Beneath that zone lies the inferior vena cava, and fatal results have followed too vigorous an aspiration without due regard to anatomy. The needle should be inserted, under local anaesthesia, at the most tender and prominent portion of the liver. If, however, there is a definite bulging of an intercostal space in the axillary line, then that should be the point of election, sometimes, however, it may be advisable to select the posterior aspect of the thorax at the angle of the scapula. In exploratory aspirations the needle should always be inserted in an upward and inward direction i.e., towards the nipple, the needle will then pass through the main structures of the liver, and will be likely to tap the abscess in the upper part of the right lobe. It will readily be seen that it is unsound to pass the needle in a strictly horizontal direction. While the needle is entering the liver, traction should be made upon the plunger, in order that any pus encountered may enter the barrel of the syringe and be recognized.

In acute cases liver abscess pus is a characteristic chocolate colour, but in long standing cases it may be thicker, of a gummatous consistency, and actually yellow. Very rarely can amoebæ be demonstrated in aspirated pus, the author has succeeded in doing so on only two occasions, though others have had better fortune, for S. M. Chen, G. W. Van Gorder and Y. K. Yuan (1931) found amoebæ in twenty six out of forty cases. The amoebæ usually appear in the pus at the end of aspiration as they are situated actually in the walls of the abscess cavity. The microscopic characteristics of the pus may be (1) many disintegrating leucocytes, (2) hepatic cells undergoing fatty degeneration, and (3) cholesterol crystals. It is usually sterile on culture, but in longstanding cases streptococci and *Bacillus coli* may be present.

H. L. Chung *et al* have described a novel method by aspiration injection of air and 10 c.c. of lipiodol which sinks to the bottom of the cavity and, with air floating above it, reveals the size and shape of the cavity by X rays or fluoroscopy. By these means it is found that the actual healing of the liver damage may be a matter of weeks or even months.



**Liver-function tests.**—The value of biochemical tests in indicating involvement of liver function has been emphasized by A. F. Hurst. In this connexion the author's attempts to utilize the laevulose tolerance and the Iromsulphthalein tests have shown them unreliable.

### TREATMENT OF HEPATIC AMOEBIASIS

Acute amoebic hepatitis (or hepatic amoebiasis) reacts very quickly to emetine injections given in the generally accepted dosage. The

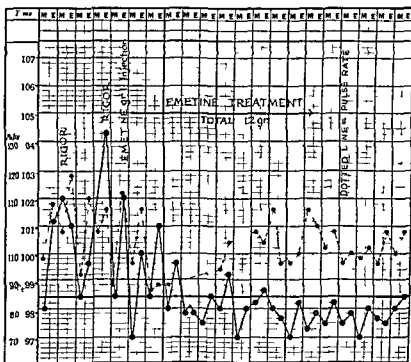


Chart 8 — Acute hepatic amoebiasis showing immediate effect of emetine injections. The dotted line represents the pulse rate.

improvement is noticeable after the injection of 2–8 grains. Subsequently routine anti amoebic treatment should be given. (Chart 8)

Chronic hepatic amoebiasis is also amenable to anti amoebic treatment especially to injections of emetine or the administration of ipecacuanha powder. Aperients such as the sulphates should be used cautiously and the patient should be placed on a low dietary. The liver is poulticed by hot fomentations and antiphlogistine and if there is much pain dry cupping may be resorted to or leeches may

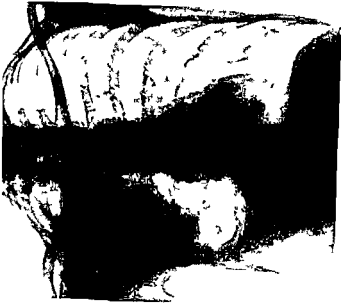


*Photo D. G. Maher, Cornell*

Radiograph of dome of diaphragm in amœbic abscess of liver

**AMŒBIC ABSCESS OF LIVER**

**PLATE X**



*Photo by G. Mather Condon*

Left, Pleural effusion into right pleural cavity, associated with liver abscess. After aspiration, the pleural effusion disappeared and the site of the abscess was marked by a gas vesicle.  
Right, Transdiaphragmatic rupture of liver abscess into right lung, with expectoration of liver-pus

## AMOEBIASIS OF LIVER

PLATE VI

be applied over the affected area. Ammonium chloride in 20 grain doses three times a day appears to have the effect of reducing it.

There has been considerable controversy about the effect of emetine and E. B. I. in the treatment of *hepatic abscess*. In the author's opinion, there are undoubtedly cases in which the physical signs of liver abscess and the accumulation of pus have disappeared upon intense anti amoebic treatment, but this is by no means always the case. The possible explanation of this will be given later.

Can a liver abscess always be aborted or prevented from forming by routine treatment with emetine bismuth iodide? Since the adoption of E. B. I. and quinoxyl as the stock treatment for all cases of chronic amoebiasis, failure has once been recorded among the author's cases.

This concerned a man of fifty eight who had spent forty two years in West and Central Africa. In 1925 he had been operated upon for acute appendicitis, and he subsequently suffered from hepatitis and was said to have developed a liver abscess which was controlled by emetine injections. *E. histolytica* were found only once in the faeces, in January, 1934, when amoebic ulcers were demonstrated in the bowel by sigmoidoscopy. During the nine years he had suffered from time to time from febrile attacks which were controlled by injections of emetine, liver abscess had been suspected but X ray examination of the liver and gall bladder had failed to reveal any abnormality, while his general health had remained excellent and he had continued to put on weight. The only suspicious feature was a persistently high leucocyte count of 11,000. He was then given a thorough course of E. B. I. and quinoxyl lasting twelve days.

On his return to Rhodesia he remained well for a year, then the febrile bouts recommenced, and in October, 1935, he returned to have an exploratory laparotomy performed for suspected cholecystitis. In November, 1935, a chronic intralobar hepatic abscess the size of an apple was found in the posterior part of the right lobe of the liver, where it was very difficult to locate and approach. It was drained, and four ounces of pus escaped. Convalescence lasted eight weeks but was retarded by the intervention of an attack of amoebic dysentery with blood and mucus in stools containing numerous active *E. histolytica*, and later by a *B. coli* bacilluria. The dysentery was controlled by a further course of E. B. I. and quinoxyl and the bacilluria by mandelic acid treatment. The patient finally recovered and has remained free from any symptom of amoebiasis ever since.

When rigors are present or when there are signs of bulging or oedema, medicinal treatment is of little value, and steps must be taken to aspirate pus from the liver.

**Aspiration**—Aspiration of liver pus by means of Potain's aspirator has received much support. It must, however, always be preceded by preliminary aspiration. Local anaesthesia (2 per cent novocain) is usually sufficient, but general narcosis is advisable in nervous subjects. A medium or full sized aspirating needle is used, as the pus may be too thick to flow through a cannula of smaller bore. Yellow serous fluid suggests a pleural exudate, especially when fibrin is present, and may indicate an underlying hepatic abscess. Sometimes, even

when no pus is found, great improvement follows the aspiration of several ounces of blood from the liver (*hepatic phlebotomy*)

The closed, or aspiration method of evacuating liver pus is no new procedure. It was advocated as long ago as 1828 by Annesley, and was used in 1871 by Maclean by means of the Bowditch syringe. In 1883 Manson devised his well known trocar and cannula in order to drain liver abscess. In 1902 Sir Leonard Rogers advocated repeated aspiration of the hepatic abscess, and injection of quinine in solution as an amoebicide.

The records of the British Army in India in the closing days of the last century are very impressive. Out of 2 661 cases treated by open operation, the mortality was 56·7 per cent. This was before aspiration methods had been generally adopted. Since that time, out of 111 cases collected from various sources, which were treated by aspiration alone, the mortality has been shown to be less than a quarter of that figure.

The advantages of using Potain's aspirator are many, the death rate has been reduced considerably, the shock to the patient is negligible, and several pints of pus may be evacuated. When anti-amoebic treatment is instituted recurrence in the majority of instances, does not take place. When pus has been found by exploratory puncture, the aspirating needle is inserted along the same track and pus will flow when the stop cock of the exhaust bottle is turned. Should the pus prove to be too thick for aspiration it may be diluted by injection of weak eusol solution into the abscess cavity. The method is so simple that it may be practised in the patient's room in the absence of the facilities offered by an operating theatre.

Sometimes almost incredible quantities of pus are aspirated. The author has frequently obtained 40-60 oz. but in one reported by A. C. Alport and F. Ghahoungui 3 500 c.c. (120 oz.) were removed by one aspiration. The total amount was 8 100 c.c. (270 oz.) in four aspirations. The liver therefore showed itself capable of accommodating nearly one and a half times its volume of pus without rupturing.

Usually an effusion of serum takes place into the abscess cavity immediately after the aspiration, and the swelling and pain thus produced may give rise to symptoms simulating a re-accumulation of pus. Likewise a passive effusion of serum into the pleural cavity sometimes occurs. Usually the passage of the needle through the liver is painless.

The author regards aspiration by Potain's method as the method of election. In his series 47 per cent. of cases were cured by one aspiration but in three cases a second or even a third had to be performed. There is a certain risk of hæmorrhage after multiple punctures by this method, but unless the liver substance is actually lacerated, there appears to be little danger. Whenever possible, 3 or 4 grains of emetine should be injected hypodermically three or four

days before aspiration, as this procedure definitely lessens the risk of subsequent hæmorrhage

A thorough course of E B I and quinoxyl should be given as a sequel to aspiration, especially in those cases in which there are *E histolytica* cysts in the faeces. The following is a typical instance of this procedure

A ship's engineer was seen in November, 1932. He had suffered four months previously from amœbic dysentery, and had been treated on board ship as November 1932

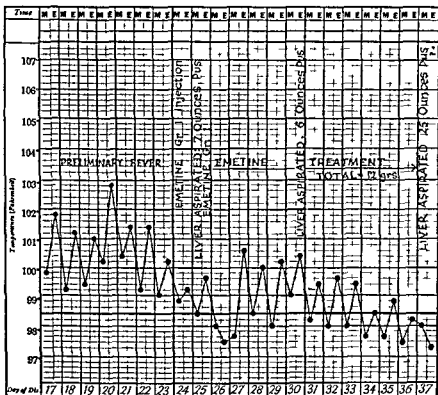


Chart 9 —Amœbic abscess of liver, to show effect of the combined aspiration and emetine treatment. The result was successful

a case of pleurisy, on account of right sided pain. The signs and symptoms of liver abscess were fairly definite and were confined to the liver and base of the right lung, shoulder pain was also marked. The X ray examination revealed typical doming of the diaphragm, and a leucocytosis of 15 000 was found. Aspiration by Potain's method in the eighth intercostal space in the mid axillary line, resulted in the withdrawal of 45 ounces of pus. Almost immediately the fever ceased and signs and symptoms disappeared. An after course of combined E B I and quinoxyl treatment was given, and the patient left hospital looking well and strong after thirty two days. There has been no recurrence since (Chart 9)

**The open operation.**—Only occasionally at the present time has resort to be made to open operation and drainage of liver abscess. In longstanding cases the pus may be so thick, and the necrotic tissue in the wall of the cavity so abundant, that the only means of evacuating it is thorough drainage and irrigation by the Carrel Dakin method. Secondary infection is the most important indication for this method.

A C Alport and F Ghaloungui (1939) think that the modern practice should be to aspirate the abscess before operation, stain a smear of pus, and examine for bacteria and, when *B. pyocyaneus* or other organisms are present, to give sulphonamide 2 grm. for 10 days, with injection of soluceptaine into the abscess cavity.

**Transperitoneal route**—When pus is struck below the costal margin, the exploring needle is left *in situ* and the abdomen is opened at this site, the intestines being protected with packing. If adhesions are present they are divided, and sinus forceps are directed along the needle and pushed through to the abscess, the blades are opened after withdrawal of the needle. A suction apparatus minimizes the risk of soiling.

The finger is inserted into the abscess cavity, and when the first gush of pus ceases the exit is lightly plugged with gauze, and the margins of the liver wound are carefully sutured to those of the parietal peritoneum, the remainder being closed. The gauze plug is now removed, and a wide drainage-tube, provided with a flange and lateral opening is introduced to the bottom of the abscess cavity. This approach is useful for multiple abscesses and for those extending anteriorly and to the left lobe. It is undoubtedly the safest method of approach.

**Transpleural route**—Should the abscess be found through an intercostal space, a few inches of rib are resected. The diaphragm should then be stitched to the thoracic wall, when the abscess may be opened by passing a pair of forceps through the pleura. An attempt should be made to stitch the capsule of the liver to the diaphragm. Should the pleura be opened, pneumothorax will result, but this is not necessarily a serious accident. On no account should pus be permitted to enter the pleural cavity. If pleural and peritoneal adhesions are not present, it is usually advisable to pack the cavity with gauze and complete the operation in two days time. The two stage method is advisable when using this route.

The following case is cited as showing the necessity of obtaining thorough and efficient drainage after operation.

A man who had lived in the Transvaal all his life was seen in January, 1931. In March, 1930, he had suffered from 'dysentery' and had been treated by emetine injections in South Africa. He came to England in June, 1930 and in November of that year was taken suddenly ill, with high fever, nausea and vomiting.

In December, 1930 he was admitted to a London hospital, where enlargement of the liver was recognized also involvement of the base of the right lung. The leucocytes numbered 14 758. After a preliminary aspiration of

500 c c of pus open operation was performed and a tube inserted into the abscess cavity. Active *E. histolytica* were found in the pus but there was no response to treatment with E B I (19 grains).

The recovery of this case after admission to the Hospital for Tropical Diseases on March 19 1931 was due to the establishment of free drainage. On re opening the wound in the seventh intercostal space in the mid axillary line, 10 ounces of claret like pus were evacuated.  $1\frac{1}{2}$  inches of the eighth rib were resected and the cavity was explored and thoroughly washed

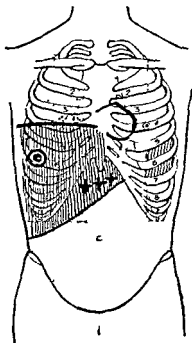


Fig. 39—Liver abscess of anterior surface of right lobe. South African infection.

\*Signs at base of right lung. no *E. histolytica* cysts in faeces. leucocytes, 91 000. Open operation, 40 fl. oz. of pus evacuated. secondarily infected with *Bacillus coli*.

⊙ site of abscess. +++ maximum tenderness.

out with normal saline. A rubber drainage tube was inserted and the Carrel Dakin method of continuous drainage instituted. Rapid convalescence took place. No *E. histolytica* cysts were found in the faeces after repeated examinations but they were discovered a year and a half later necessitating a combined course of E B I and quinoxyl (Fig. 39).

Necrosis of one or more ribs in the vicinity of the drainage-tube is a not uncommon event after operation for hepatic abscess. Lecomte (1918) has described six cases and thinks that this complication is more frequent in those instances where the abscess has been opened without resection of a rib and that it is caused by insufficient drainage.



or, it may be, by pressure of the drainage tube. The necrosis usually affects the anterior part of the ribs and their cartilages.

**Treatment after operation**—For the first two days after a liver abscess has been opened the discharge is considerable, and the dressing may have to be changed frequently. Very soon, however, should the case do well the discharge diminishes, and the dressing requires renewal every other day or every three or four days. During the first week the drainage tube, provided it be acting efficiently, should not be disturbed more particularly as it may be difficult to replace. Later it may be removed and cleaned and when discharge has practically ceased, cautiously shortened. *It is a great mistake to begin shortening the tube before it is being pushed out or so long as there is any appreciable discharge.* If there is the slightest indication such as rise of temperature, that pus is being retained the sinus if necessary, must be dilated with forceps and finger and a full sized drainage tube introduced as far as it will go. If this does not suffice a counter opening may have to be made. *Delay in remedying imperfect drainage is serious and it may be fatal.*

Should an abscess on being opened be found to be secondarily infected or should it become so it must be flushed out daily with a weak non mercurial antiseptic and a counter opening made if necessary. Continuous drainage by the Carrel Dakin tube method and daily eusol irrigation is often very successful.

After a liver abscess has been opened and is draining well the temperature rapidly falls and in a few days becomes normal. Should fever persist it is to be inferred that the drainage is inefficient, that there are other abscesses in the liver or that some complication has arisen. If another abscess is suspected it should be sought with the aspirator and drained.

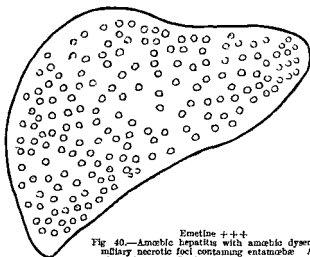
It is advisable to give emetine hypodermically in 1 grain doses both before and after the operation and to continue to exhibit it for a fortnight.

If any symptoms of hepatic inefficiency due to extensive destruction of liver tissue are noted the presence of diacetic acid or a high ammonia coefficient in the urine should be an indication for the oral or rectal administration of glucose and sodium bicarbonate or in some cases for intravenous injection in 5 to 10 per cent solution.

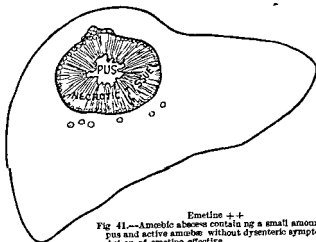
After evacuation, a Carrel's tube is passed inside the larger drainage-tube and irrigation with Dakin's solution is carried out by means of a large glass syringe at two hourly intervals for nineteen days. A preparation containing ferments (Enzymol Fairchild) half an ounce to an ounce of water is useful for injection into the abscess cavity for dissolving adherent sloughs.

**Indications for emetine treatment**—It is necessary that some hypothesis be formulated as to the rationale of these various methods of treatment. Most authorities recognize that emetine has a selective

action in acute amœbic hepatitis which occurs in the course of amœbic dysentery. In amœbic hepatitis numerous small necrotic foci containing 'nests' of amœbæ form in the liver (Fig 40). It is reasonable to suppose that emetine therapy extirpates these and that the surrounding necrotic tissue is absorbed. These considerations are based upon the observed fact that the alkaloid—emetine—has a selective action upon the trophozoites of *E. histolytica*, while E. B. I. exerts a special action upon cysts.



Emetine +++  
Fig 40.—Amœbic hepatitis with amœbic dysentery  
miliary necrotic foci containing entamœbæ. Action  
of emetine very effective



Emetine ++  
Fig 41.—Amœbic abscess containing a small amount of  
pus and active amœbæ without dysenteric symptoms.  
Act on of emetine effective

Figs 40, 41 —Diagrams to illustrate the formation of amœbic abscess of the liver

The next stage in the formation of a liver abscess, which may be termed the early suppurative stage, is less acute. Here the necrotic tissue, which has been liquefied by the action of the amœbæ, is sterile (Fig 41). The amœbæ living in the actual abscess cavity are still in an active state of multiplication and are vulnerable to the action of emetine. Small intrahepatic abscesses yield rapidly to emetine therapy and the necrotic tissue becomes absorbed into the body without necessitating free drainage.

In the third stage, the abscess cavity contains a fairly large quantity of sterile pus (½–1 pint) and its walls are lined with necrotic tissue containing active amœbæ (Fig 42). It is at this stage that aspiration

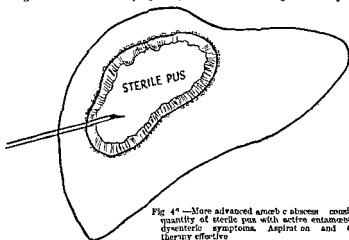
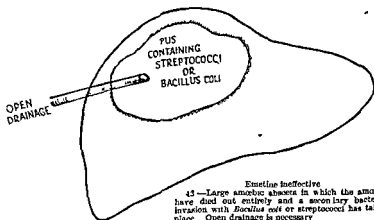


Fig 42—More advanced amœbic abscess—considerable quantity of sterile pus with active endamoebæ. No dysenteric symptoms. Aspiration and emetine therapy effective.

Figs. 42, 43—Diagrams to illustrate the formation of amœbic abscess of the liver.



Emetine ineffective

43—Large amœbic abscess in which the amœbæ have died out entirely and a secondary bacterial invasion with *Bacillus coli* or streptococci has taken place. Open drainage is necessary.

combined with emetine therapy is effective. The amount of pus is too large to be absorbed, and the amœbæ in the abscess cavity are vulnerable to the action of the emetine.

In the final stage, the abscess cavity has grown to a large size and the active amœbæ have died out, because conditions are unfavourable to their further multiplication. A similar process takes place in gummata of the liver and in tuberculosis in which diseases also the causative organisms eventually disappear.

As a rule, in longstanding amœbic abscesses secondary infection

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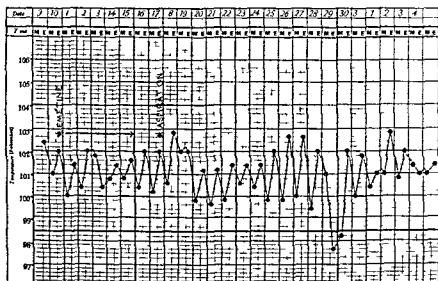


Chart 10 — Fatal case of amœbic abscess of the liver. Rupture into the right lung. Death from streptococcal septicæmia. Failure of emetine and aspiration therapy.

with micro organisms takes place, and when this has occurred, emetine therapy can no longer have effect. Open free drainage now becomes imperative, in order to evacuate pus, the tube being sufficiently large and perforated to afford efficient and continuous drainage (Fig 43).

### PROGNOSIS OF HEPATIC ABSCESS

Under modern conditions, with early operative interference and with emetine and EBI therapy, the prognosis is good in cases of single abscess. In multiple abscesses, however, or in a single abscess if it is loculated, it is by no means so good and if there are more than two or three abscesses, it is usually hopeless.

If partial rupture into the lung takes place, there is danger that the original abscess cavity may become infected with streptococci, and

that eventually a streptococcal septicæmia may result (Chart 10) The following case illustrates this point.—

A mining engineer had suffered for nearly thirty years during his residence in India from periodical attacks of diarrhœa, but the first inklings of a liver abscess were noted on July 13, 1931, when he fell from a ladder on his left side. His illness then commenced with diarrhœa and a high temperature, which was at first suspected of being typhoid or malaria. Liver abscess was definitely diagnosed on October 9, when he was admitted to hospital. Repeated aspirations of the liver resulted in the withdrawal both from the lung and from the liver, of pus which was found to be heavily infected with streptococci. On October 17 an open operation resulted in the withdrawal of more pus, a partial resection of the eighth rib was made and Carrel Dakin drainage instituted. No improvement took place in spite of the administration of antistreptococcal serum and blood transfusion. Streptococcal septicæmia was diagnosed, and death took place on January 1, 1932.

At the autopsy three distinct abscesses were revealed—all situated in the right lobe of the liver, one was healed and one in the process of granulation, but the third, which had not been touched by any of the operative procedures, contained a pint of pus and involved the posterior portion of the right lobe. Extensive compensatory hypertrophy of the left lobe of the liver was present. A left subdiaphragmatic abscess was found in the subphrenic space. In the right lung there was a small loculated empyema situated posteriorly. The spleen was greatly enlarged and soft but no macroscopic evidence of amœbic ulceration of the large intestine was found (See Fig 29, p 210).

The question of return to the tropics after recovery from liver abscess is a matter that frequently has to be decided. If a relapse of the amœbic abscess has occurred during treatment, or if very considerable damage to the liver tissue has taken place, the patient should remain in a healthy and temperate climate. But there are many instances of patients who have enjoyed permanent good health in the tropics after recovery from liver abscess. Before giving permission for the patient to return it must be ascertained by repeated sigmoidoscopy and examinations of the feces, that the bowel is thoroughly cleared of amœbic infection. Through neglect of this precaution, re-infection of the liver from the bowel may occur. Recurrences of liver abscess have been known after periods as long as from five to seven years from the formation of the first.

## CHAPTER XV

### AMŒBIASIS (*continued*): RARER AMŒBIC LESIONS

#### AMŒBIC ABSCESS OF THE LUNG (PULMONARY AMŒBIASIS)

As a general rule, amœbic abscess of the lung is secondary to abscess of the liver, but primary pulmonary amœbic lesions have rarely been described. Usually they are single, but they may be small and multiple. The lower lobe of the right lung is the part usually involved, and the diaphragm becomes adherent to the lung as well as to the liver. Rupture takes place into the bronchus and the pus is then expectorated.

*Microscopic pathology*—The inner surface of the abscess wall consists of a zone of necrotic material containing histolysed lung cells, amœbæ, a few polymorphonuclear leucocytes, and many lymphocytes.

In most cases of amœbiasis in which the lung is affected, direct extension of a previously existing hepatic abscess through the diaphragm can be proved to have taken place. Rupture of an unrecognized liver abscess into the lung may produce the most varied pulmonary symptoms, so it is not surprising that when such an accident takes place, other more familiar conditions of the lung are first envisaged. Extension of an hepatic abscess into the lung—or *secondary pulmonary amœbiasis*—may simulate bronchiectasis or unresolved pneumonitis (Plate XI, right, facing p. 235).

The author has records of instances of this complication, in two of which the diagnosis of tuberculosis had originally been made.

The first was a staff sergeant of the R.F.A. who originally contracted dysentery in India, and was invalided to England in 1915 suffering from dysenteric symptoms associated with phlebitis of both legs. Later he had repeated attacks of "pneumonia" in the lower lobe of his right lung which were succeeded by thrombosis of the pelvic veins with compensating enlargement of the superficial abdominal veins. In February 1920, five years and two months after the original attack, he suffered from repeated attacks of "pleurisy" accompanied by profuse blood-stained expectoration. At the time he had been thought to be suffering from pulmonary tuberculosis. On admission to hospital this diagnosis was altered by discovery of *E. histolytica* cysts in the faeces. There was clubbing of fingers and toes and the superficial abdominal veins were varicose. On intensive emetine and E.B.I. therapy, he made a rapid recovery.

A second case, seen in 1921, was similar in many ways except that no direct evidence of amœbiasis, by the presence of *E. histolytica* cysts in the faeces, was obtained. The patient was an Englishman who had resided many years

in India and had recently returned to England on leave. The signs and symptoms were mostly confined to the lower lobe of the right lung. Response to specific treatment with emetine was most striking, and in less than six months he gained 47 pounds in weight.

A lady who travelled in Chile arrived in London in May, 1927. Within two days she developed signs of pleurisy at the base of the right lung, three days later there was high fever with hæmoptysis and expectoration of blood stained, frothy pus, accompanied by acute diarrhoea. X ray examination showed a large consolidated mass in the centre of the right lung (on which a previous diagnosis of malignant disease of the lung had tentatively been made). There was, however, a leucocytosis of 35,000, and the author was able to demonstrate active *E. histolytica* in the melanic fæces. A rapid recovery took place on emetine injections (10 grains) and ipecacuanha (5 grains at night, total 60 grains) and the patient remained in good health afterwards.

A young man from Shanghai had suffered for years from dysenteric symptoms and had been invalided from the East suspected of suffering from pulmonary tuberculosis. In the autumn of 1925 he developed a violent cough with the expectoration of blood stained, purulent sputum, and a diagnosis of pulmonary amoebiasis was made on the radiographic appearances. *E. histolytica* cysts were found in the fæces and he had a leucocytosis of 20,000. On appropriate treatment with emetine and ipecacuanha a rapid recovery took place. This case was notable in that the skiagram showed the valve like flap formed by rupture of the diaphragm.

A fifth case demonstrates the complications which may occur if the condition is not recognized and suitably treated. The Quartermaster of a Regiment of the 29th Division had landed in Gallipoli in April 1915 and remained there until the evacuation in 1916. After suffering from amoebic dysentery, he developed a liver abscess which burst into his right lung in March of that year. After courses of emetine therapy, which were not successful, several ribs were resected and the liver abscess was drained in July, 1917. The sinus never healed, and the patient developed a bronchial sinus which communicated with the pleural wound. Apparently numerous pockets of pus had formed. In November, 1924, a modified Eslander operation was performed, and the sinus healed. Under prolonged emetine therapy the patient made a good recovery, and he has since remained in fairly good health.

There are various points to be noted in connexion with the diagnosis of transdiaphragmatic rupture of liver abscess. Hiccough is a not uncommon accompaniment. Chocolate-coloured liver pus is usually noted in the first portions to be expectorated, subsequently the sputum becomes more profuse yellow and frothy, and not until the abscess cavity is almost empty is it viscid and gummatous. Expectoration of liver pus causes a considerable degree of pulmonary irritation. When paroxysms of coughing occur, pus accumulates and is then evacuated in large amounts at periodic intervals. Lying on the sound lung sets up irritation, while relief is obtained by turning to the affected side. Some assistance in diagnosis can be obtained from the microscopic appearances of the expectorated pus, which usually contains Charcot-Leyden crystals, the remains of liver cells and epithelioid cells derived from the lung. Sometimes fibres derived from the muscles of the diaphragm may also be recognized.

In all cases of abscess discharging through the lung a careful record should be kept of the body temperature, the daily amount and character of the expectoration, and the weight of the patient. If the temperature remains raised, if the amount of expectorated pus is constant or increases, or if the patient continues to lose weight, an attempt should be made to reach and drain the abscess from outside, especially if there is no response to medicinal treatment after full doses of emetine and ipecacuanha. If the temperature remains normal, the pus gradually decreases, and the body weight is maintained, operation is unnecessary, or at all events should be deferred.

The X ray appearances present a well marked opacity at the base of the right lung with obliteration of the costophrenic angle and immobility of the right hemi diaphragm, appearances which in native races are apt to be taken as evidence of tuberculosis.

**Primary pulmonary amoebiasis**—In a case of primary pulmonary amoebiasis the condition is not so readily recognizable as in the foregoing. Abscess of the lung due to *E. histolytica* can occur quite independently of abscess of the liver, it is seldom recognized during the lifetime of the patient although A. C. Alport and F. Ghahoungui have demonstrated *E. histolytica* in the walls of a pulmonary abscess, and in microscopic section the organisms were seen penetrating the wall of a pulmonary artery.

Cohn in 1873 described ten abscesses of the lung which were secondary to a thrombosis in the liver, and in a case reported by Moxon the liver abscess had actually burst into a subhepatic vein and then spread to the lung. In primary pulmonary amoebiasis, the probable route by which the amoebae gain access to the pulmonary circulation is, as suggested by C. H. Bunting in 1906, by direct embolism into the lung through the circulation from the colon. In Bunting's case firm consolidated nodules were found in the lung and in each entamoebæ were demonstrated in section.

In another case, described by Opie in 1901, a large amoebic abscess was found in the right lung, there being present, also, what appeared to be a healed amoebic abscess of the liver.

Tuffier (1908) recognized the condition during life, and he is reported to have cured his patient by operative interference. In this case the abscess was situated in the right lung and hæmoptysis, fever, and other symptoms were present. Loison reported a similar instance, and suggested aspiration of the pus. The abscess cavity was outlined by means of a radioscopic screen. The same patient subsequently developed a hepatic abscess. J. W. S. Macfie (1920) found at autopsy, an amoebic abscess of the lung in association with a similar condition of the liver, the two lesions not being connected with each other, and in 1923 Ramond, Denoyelle, and Lautman recorded an interesting case in which multiple pulmonary abscesses, without ascertainable involvement of the liver, were recognized during life and all symptoms disappeared after emetine therapy. C. A. H. Dopter (1927) has given a vivid description of this complication as it occurs in French military practice.

R. W. Keeton and M. Hood gave (1938) an excellent description, illustrated with radiographs, of this complication as it occurred in Chicago.

X ray examination may not reveal any evident lesions, but B. A.



Dormer and J. Friedlander (1941) state that the radiographic appearances may resemble tuberculous infiltration or bronchopneumonic consolidation.

So far, there are no authentic instances of amœbæ having been demonstrated in the sputum, although various observers have described bodies which they thought might be dead organisms, but which probably were the large epithelioid cells usually present in inflammatory pulmonary conditions.

Three cases of primary pulmonary amœbiasis which have occurred in the author's practice are described below. All three responded in a dramatic manner to emetine and ipecacuanha therapy. It will be noted that the diagnosis of this curious condition must be based upon the previous history of intestinal amœbiasis, the leucocytosis, and lasting response to emetine therapy.

The first case was that of an ex soldier who had suffered from amœbic dysentery in 1918, and was admitted to hospital in March, 1921. He was ill and emaciated, and his main symptoms were acute pain in the lower chest on the right side, accompanied by cough, fever, and respiratory distress. Profuse purulent sputum, without hæmoptysis, was expectorated, and an intermittent pyrexia varying between 101° and 102° F. with nocturnal sweats, and a leucocytosis of 14 000 were present. No clubbing of the fingers was noted. A patch of dullness 4 inches in diameter was found below the angle of the right scapula, with bronchial breath sounds and occasional crepitations. Later, similar broncho-pneumonic areas became apparent in the lower lobe of the left lung. The sputum contained numerous pus and large epithelioid cells. No evidence of liver involvement was found. The probable diagnosis appeared to be tuberculous broncho pneumonia but as no improvement took place after a month in hospital, emetine injections (1 grain) daily, together with 10 grains of powdered ipecacuanha, were instituted. There was immediate improvement: the temperature became normal, and the patient recovered and regained 28 lb. in weight.

An ex soldier from Mesopotamia had suffered from amœbic dysentery with numerous relapses, and had been treated in hospital. Re-admitted in May, 1921, fourteen days later he commenced to suffer from rigors, together with bronchial pneumonic consolidation of the lungs, nocturnal perspiration and profuse purulent expectoration. The signs and symptoms suggested pulmonary tuberculosis. There was a slight leucocytosis of 9,000 but the feces contained no *E. histolytica* cysts. In this case also there was striking improvement following the injection of 16 grains of emetine with, later, 10 grains of ipecacuanha at night (300 grains in all). He put on 21 lb. in weight.

The third case occurred in an Indian seaman, aged twenty-eight, who showed signs of diffuse bronchial pneumonia. In this case the pulmonary signs were most evident at the base of the right lung, where a friction rub could be heard. There was a leucocytosis of 34 000, but no other evidences of amœbic infection. After three weeks in hospital on expectant treatment, no improvement was noted, but the results of emetine injections (11 grains), followed by 5 grains of ipecacuanha powder at night (70 grains) were remarkable, the temperature fell immediately and there was a gain in weight of 28 lb. X rays afforded little assistance in the diagnosis.

It is probable that these cases are much more frequent than has

hitherto been realized, their recognition having been prevented by the difficulty in obtaining evidence of associated amoebiasis

**Amoebic abscess of the brain.**—This condition is very rare and is secondary to amoebic abscess of the liver or lung. The first case was described by S Kartulis (1887). H Legrand (1912) published a paper on forty five cases of brain abscess secondary to liver abscess. They were single, and affected the cerebrum, but in one case the cerebellum.

It is by no means certain that all the recorded cases are examples of amoebic infection. According to F L Armitage, who collected all the known cases in the literature in 1919, forty eight cases had then been recorded, of which half (twenty four) occurred in Egypt. The condition is most frequently observed between the ages of twenty and forty—though a case was reported in a child of five—and it is much more common in men than in women (three cases only). None of the patients has recovered.

The abscess is described as being generally single and as occurring with equal frequency on the right and left side. bilateral abscesses have been found on six occasions. In recent acute cases there is no resulting pyogenic membrane, but in those of long standing there is a tendency to formation of a cyst wall.

The solitary case described in recent years is that recorded by T D M Stout and D E Fenwick (1918). The patient was operated on for a liver abscess, and in the discharge from the cavity active *E histolytica* were found. The result of operation was good as regards immediate relief, but in spite of emetine injections (14 grains), the pyrexia remained high, and the patient died. An abscess the size of a pigeon's egg was found in the front lobe of the brain, and in the pus *E histolytica* were present.

The differential diagnosis has to be made from cerebral malaria, metastatic septic abscess, caseating tuberculosis of the brain, cerebral gumma, and actinomycosis.

The disease is rapidly fatal, death in the recorded cases taking place on the sixth to the eighth day from the onset of headache.

**Amoebic abscesses of the spleen, epididymis and penis.**—J. Rogers has described several cases of abscess of the spleen in his records of autopsies in Calcutta, all secondary to amoebic abscesses of the liver. O Jacob (1911) collected fifteen cases of hepatic complicated by similar splenic abscesses.

Amoebic abscess of the epididymis has once been reported. The case was described by A S Warthin (1922) from China, in a patient suffering from chronic amoebic dysentery. The epididymis showed dilatation of the ducts, in which masses of spermatozoa and numerous amoebae were demonstrated.

H F Shih, J K Wu, and V T Lue (1939) described an amoebic ulceration of the penis, of five months duration, healed by emetine injections.

**Amœbic infection of the skin and other tissues**—It appears that under certain circumstances invasion of the skin by *Entamoeba histolytica*, producing extensive destruction and sloughing of the tissues, may take place in the vicinity of a discharging amœbic abscess of the liver, or in immediate proximity to the bowel.

L Tixier, M Favre, E Morenas, and C Petouraud (1927) have described in minute detail a perianal lesion in a man suffering from chronic dysentery. It had been present for six years, but healed rapidly after emetine injections. In the pus *entamoebæ* were found. Examination revealed microscopic, punched out ulcers of the epidermis, and of deep seated colonies of amœbe.

M F Engman and H E Meleney (1931) found amœbæ in ulcers of the skin and deeper tissues of the abdominal wall. One ulcer was secondary to an operation for resection of a portion of the colon involved in amœbic ulceration, the other followed drainage of an amœbic abscess of the liver. Clinically, the skin lesions showed a rapidly spreading ulcerative process and a border presenting irregular outline. There was extreme pain on pressure, and the floor of the ulcer was composed of granulation tissue covered with débris and pus.

S T Ngai and C N Frazier (1933) made a careful and complete survey of the literature of this subject since 1891, together with a detailed clinical and histological report of three cases in Peking. They also first described amœbic ulceration of the urethra. One of the best cases is that described by L F Heimburger (1925). The patient suffered from a tumour in the right lumbar region which discharged liver pus, and from that time an ulcer developed in the mid axillary line, which exuded foul pus. Amœbæ were demonstrated in stained sections of the tissue from the edge of the ulcer. Under emetine therapy the pyrexia remitted and the ulcer healed rapidly.

A case of deep gangrene with extensive tissue destruction in which large numbers of *E. histolytica* were demonstrated has been described by F L and H E Meleney (1935). Though the patient had diabetes, response to emetine therapy was almost miraculous. The author (1937) has had a somewhat similar case of ulceration of the abdominal wall with massive destruction of the parietes (Figs 44, 45), emanating from a colostomy opening in a case operated upon for suppo-ed carcinoma of the rectum. Symptoms and signs of active amœbiasis were present and *E. histolytica* were found in numbers in sections of the skin (Fig 46). Amœbic ulcers were visible on the exposed loop of bowel. The response to emetine therapy was very striking so that after 8 grams all signs of sloughing had disappeared. A more dramatic and almost terrifying destruction of the perineum and abdominal wall (1938) occurred in St Mark's Hospital, London (W B Gabriel), here the tissues of the abdominal wall as well as the buttocks were involved and the man's life was undoubtedly saved by emetine injections. Though the patient had served fifteen years previously in the Army in India and had

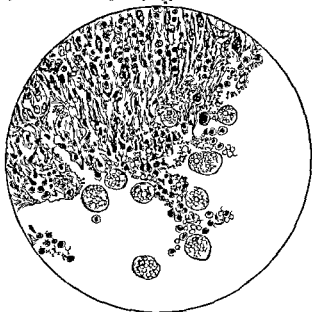


Fig. 44.—Amœbic granuloma and ulceration of the abdominal parietes surrounding colostomy.



Fig. 45.—Amœbic granuloma and ulceration of abdominal parietes surrounding colostomy. Appearance after injection of 8 grains of emetine.

*E. histolytica* cysts in the faeces he had never suffered from diarrhoea or dysentery. The primary lesion appears to have been a perirectal abscess. A left iliac colostomy was performed. In spite of irrigations, ulceration spread relentlessly to the perineum, sacrum and also on the abdominal wall round the colostomy wound. The patient was extremely ill with hectic fever and tachycardia. There was an enormous ulcerating cavity which had destroyed the rectal floor. Response to emetine was instantaneous. After 8 grains the cavities had granulated up and the amœbic infection was cured by EBI and quinovyl. Thiersch grafts were subsequently applied.



P H M B

Fig. 46—Section of amœbic skin granuloma showing invasion of subdermal tissues by *Entamoeba histolytica*.

C. H. Hsu (1937) in Peiping, China, described a series of fourteen cases and in his opinion the condition is by no means rare. Amœbiæ cutis occurs chiefly as an unsuspected secondary infection of papillomata usually of the anal region. The lesions generally take the form of characteristic punched out ulcers implanted upon perianal papillomata, in the urethra on condylomatous growths of the anus and vulva, even situated in the cervix on carcinomata of that region as well as on papillomata of the labia majora and minora. These ulcers are aptly termed by the French workers Tixer et al (1927) *poroderme amibienne*. The lesions produced are fundamen-

R V Rajam and P N Rangiah (1939) have described amœbic anal ulceration and stricture of the anal orifice which was cured by emetine and E B I

The histopathology of these lesions demonstrates the destructive action of the amœbæ; once they have reached the epithelium, the cells are progressively dissolved, so that punched out ulcers are produced. There is a sero fibrinous and cellular exudate which becomes necrotic on account of a lytic action of the amœbæ.

Skin lesions produced by *E histolytica* have also been recorded by A Carini (1912), M F Engman and A S Heithaus (1919), Van Hoof (1920), and S Crawford (1933)

**Urinary amœbiasis.**—Numerous observers have reported infection of the human bladder by *Entamœba histolytica* and appearance of this organism in the urine. The evidence in the great majority of cases is very unsatisfactory, large inflammatory cells from the bladder wall, or from the prostate, often being mistaken for *E histolytica*. In the author's experience *E histolytica* cannot survive in urine for any length of time. Considerations such as these are entirely lacking from the many uncritical papers which have appeared on this subject especially one by K D Manohar.

Usually the presence of a fistulous opening between the bowel and the bladder causes the parasite to appear from time to time in the urine. In 1911 C F Craig recorded a case in which *E histolytica* were found in the urine of a patient suffering from a fistula between the bladder and an ulcerated area in the intestine.

## CHAPTER XVI

# BALANTIDIASIS, GIARDIASIS, FLAGELLATE DIARRHŒA, INTESTINAL COCCIDIOSIS, MALARIAL AND LEISHMANIAL DYSENTERIES

## BALANTIDIASIS

**Synonyms** —Balantidiosis, Balantidial dysentery Ciliate dysentery

For the past fifty years it has been recognized that a form of diarrhœa or dysentery may be caused by a ciliate protozoan—*Balantidium coli*. This is a common parasite of the domestic pig and of monkeys, and in these it may occasionally cause a fatal form of dysentery.

This parasite was probably originally seen by A. Leeuwenhoek (1672) but it was first discovered in the stools and bowels of man and accurately described by P. H. Malmsten (1857). He knew the protozoan as *Paramacium coli* and R. Leuckart in his textbook (1879-86) used the same terminology. The works of J. Mitter (1891) and B. Collman (1901) deal mostly with the human aspect of the disease while J. Shegalow (1899), J. D. McDonald (1922) and R. W. Hegner and W. H. Taliaferro (1924) have made thorough morphological studies of the balantidia of the pig. P. Bode (1923) and J. D. McDonald (1922) have endeavoured to differentiate between the human and porcine varieties. Attention has been drawn to the disease in apes by E. Christeller (1922) and H. Ziemann (1925) with special reference to clinical and pathological findings. F. Pritze (1924) has summarized much of the knowledge of this subject in a thesis for Berlin University.

**Ætiology** —*Balantidium coli* is a large intestinal ciliated protozoan and can be detected with comparative ease with a low power lens (Fig. 47). For a full description see Appendix, p. 546.

Since it was recognized that *Balantidium coli* is a common parasite of the pig it has been generally supposed that infection is conveyed to man by that animal in which it lives as a harmless commensal. Human cases have occurred in people who have been closely associated with it i.e. in pig feeders, swine herds and pork butchers but most experiments directed to infecting man from pigs have failed. O. Casagrandi and P. Barbagallo (1895) who tried to infect themselves by swallowing suitable material were unsuccessful.

A. Seira (1931), in Porto Rico, records that in over 5 000 stool



Fig 47 — *Balantidium coli* in faeces

(Photomicrograph Dr H A Griffin (over Miss Hos) Assut Egypt)

examinations *Balantidium coli* was seen only four times and that in only one were dysenteric symptoms noted

**Geographical distribution**—Cases have been recorded in the following localities —

<i>Europe</i>	England (one case) France (five) Russia Scandinavia Finland Germany (especially East Prussia) Austria Holland Italy (four in children in Calabria Sicily) Spain Georgia (Tiflis)
<i>Asia</i>	Siberia (Port Arthur) China (Tsingtau Trembur) Philippines Siam India (Assam) Marianne Islands Cochin China Sandwich Islands Andaman Islands
<i>Africa</i>	Egypt (Alexandria) Sudan.
<i>North America</i>	Seven in mental defectives in S Carolina (M D Young 1939) two from Tennessee (H E Meleney)
<i>South and Central America</i>	Brazil (Rio de Janeiro) Porto Rico Cuba

L Brumpt (1909) summarized the distribution of this parasite and Dopfer (1924) has enumerated 232 cases among whom were 143 Europeans. D L Mackenzie and H Bean (1939) recorded the first case in Great Britain in a mental patient

**Pathology**—Fatal infections are found in man as well as in monkeys. The researches of M Askanazy (1903) R Strong and W E Musgrave have shown that the balantidia penetrate into the bowel wall in the



same manner as *F. histolytica* and in the blood vessels of the mucosa and submucosa. Infection with these organisms produces primarily a hyperæmia of the bowel wall, punctiform hæmorrhages and follicular swellings with over production of mucus. Long standing ulcers are usually blackish, recent ones irregularly shaped with undermined edges. The organisms apparently penetrate the bowel wall by invading the gland ducts, dissolving the muscularis mucosæ by cytotoxicity (Fig 48). Gleesner (1908) found that they secrete a strong diastatic ferment.



Fig 48 — Microscopic section of the large intestine in human balantidiasis showing the position of the balantidia in the submucosa.

Histologically there is little to distinguish the ulcerated bowel from anæmic ulceration, but the organisms have been found by F. Martini (1910) and F. L. Waller (1913) in the mesenteric glands. A similar pathological condition has been described by E. Christeller in chimpanzees in the Berlin Zoological Gardens. E. de S. Campos (1924) has traced the method by which the ciliates enter blood vessels in the neighbourhood of the lesions. The ulcerations of the bowel as seen by sigmoidoscopy closely resemble those of intestinal amebiasis as described by S. Mazza, C. A. Alvarado and K. Schürmann (1930).

**Symptomatology.**—The symptoms produced by the balantidium in man are, as far as we know, almost indistinguishable from those of amœbic dysentery. In balantidial colitis there is colicky pain, slight abdominal tenderness, loss of appetite, thirst, furred tongue, inelastic skin, and distended abdomen. The sigmoid colon is usually sensitive and palpable, and eight to fifteen stools are passed during the day. There may be cachexia and anæmia. The stools are porridgy, fluid, feculent, alkaline in reaction, and contain remains of undigested food mucus, often stained green, and sometimes blood corpuscles and leucocytes. Occasionally, according to E. Behrenroth (1918), they contain eosinophil cells. The blood usually shows no significant change; there is no leucocytosis and the polymorphonuclears number 70 per cent.

This infection has been observed to persist, on an average, from four to fifteen years.

**Treatment.**—From experimental work, E. L. Walker (1913) concluded that organic compounds of silver were most effective in eradicating the infection, but in actual practice these preparations have not been found useful.

At present therapy is purely empirical. The following drugs have been employed: thymol as in ancylostomiasis, calomel, carbolic acid in pills, extract of filix mas, methylene blue, ipecacuanha, emetine, quinoxyl, oil of chenopodium, stovarsol and santonin. Enemata of iodine solution 1:10 000 and tannin 1:1 000 with 10–15 drops of tincture of opium and of quinine have also been used.

N. Kipschidse (1928) reports that during four years twenty-two cases of *Balantidium coli* infection have been treated in hospital in Tiflis, of which three came to autopsy. He found that emetine injections in large doses—0.05–0.06 gramme in fifteen to twenty injections—gave the best results. Good results from this drug are also reported by A. Luger and L. Korkes (1928).

E. C. Cort (1928) reports that following the suggestion of C. W. Mason (1919), he treated twelve cases in Siam by enemata of 15 c.c. of oil of chenopodium in 150 c.c. of olive oil, and all patients remained free from *Balantidium coli* thereafter. In one case a second treatment within twenty-four hours of the first brought about symptoms of chenopodium poisoning.

H. F. Onkiahong (1929) finds santonin—25 mgm. three times daily on two consecutive days—effective. L. C. D. Hermitte, S. C. Sen Gupta, and T. N. Biswas (1926) expatiate on the good results obtained by stovarsol treatment, the drug being given in the usual dose of 4 grains.

D. Yered tried a new remedy, Carobinase, a watery extract of *Jacaranda decurrens*, 25 grammes in 500 c.c. of hot water, as a rectal lavage for three weeks. There was great improvement in the patient's condition, and a definite cure was established.

A correspondent reports that in his case, in Egypt, all the parasites

disappeared from the stool after three treatments of carbon tetrachloride of 1 drachm (1 teaspoonful) each

D L Mackenzie (1938) treated his English case satisfactorily with 2 pints of methylene blue solution by enema

A Westphal (1939) employed Acranil—the hydrochlorate of acridine—in one case and found that it caused apparent disappearance of the parasites from the faeces

## GIARDIASIS

### Synonym—Lambliasis

Of the protozoan flagellates that inhabit the bowel of man, *Giardia intestinalis* has the best claim to be regarded as pathogenic, though authorities are by no means agreed upon this subject

**Ætiology**—This flagellate was first seen in 1681 by Leeuwenhoek, through his primitive microscope in his own excreta. It was re-discovered by Lambl in 1859 and was known for a long time as *Lamblia* (Blanchard, 1888), but it was eventually found that Kunstler in 1882 had established the genus *Giardia* for a species in tadpoles. Flagellates of the genus *Giardia* are found in mammals and reptiles, the species peculiar to the mouse (*G. muris*) being apparently closely allied to that found in humans

Children appear to be more commonly affected than adults, F W Bach and K H Kieffer found that, in a district in Germany where 25–27 per cent of the children were infected, only 9.7 adults were in a similar condition

Some authorities consider that the number of this parasite in the faeces depends upon the diet of the host for R Hegner (1924), and later C D de Langen (1927) found that it disappeared from the intestinal canal of infected animals fed upon meat. The parasite has been found by intubation in the duodenal juice (E Libert and G Lavier, 1923) but there appears to be no conclusive evidence that it is in any way connected with disease of the biliary apparatus. According to W C Boeck (1927) there is only one instance in which it has been found in the gall bladder at operation (L Winkler). Moreover, in children, gall bladder disease is extremely rare yet *Giardia* infection is two to three times as frequent as in adults. E A Baumgartner (1926) found these parasites in some persons who had disease of the gall bladder, but they were not found in two who submitted to operation

J J Spantenberg and colleagues investigated one case with clinical diagnosis of cholecystitis in whom active *Giardia* were on several occasions demonstrated by intubation, but not in the excised gall bladder. It seems evident that its presence in the duodenal juice in a patient suffering from biliary disease affords no indication that *Giardia* is responsible for the clinical condition. Similarly this parasite may be demonstrated in the fasting gastric juice as in the author's case during routine investigation

The morphology of *Giardia* is described in the Appendix (p 542)

**Geographical distribution**—The following are the countries of origin in a series especially studied by the author. The cases have been derived from almost all over the world. India (8), Ceylon (5), China (2), coast of West Africa (4), Nyasaland (1), South Africa (2), East Africa (3), Siam (1), Malaya (1), Iraq (1), Cape Verde Islands (1), Brazil (1), and Singapore (1).

**Pathology**—Numerous investigators have brought forward evidence of the pathogenicity of this parasite and have contributed the following information. (a) It is found in its active state and in the largest numbers when the stools are liquid and diarrhoeic. (b) In the early stages symptoms of gastro enteritis are present, while in the chronic stages stools have characteristic features and contain large numbers of the cysts (F. W. O'Connor (1919)). (c) H. E. Whittingham (1923) considers that suspicion of pathogenicity is strengthened by frequent passage of mucus in stools containing parasites in large numbers. (d) D. L. Heubner (1930), in his study of giardiasis as a distinct entity, has recorded 173 cases in Germany; he considers that, as a rule, the parasite multiplies to such an extent in the small intestine that sooner or later it must give rise to symptoms. At first it colonizes the duodenum and may beset the mucous membrane so closely that disturbance of intestinal function is produced. (e) R. Miller (1926) in a study of chronic enteritis in children found that in English children the results of the infection resemble coeliac disease more closely than any other disorder. There is persistent diarrhoea and some enlargement of the abdomen, with retardation of growth and he considers that the stool in *Giardia* infection resembles that of chronic enterocolitis. Diarrhoea was noted by H. Perkins (1921), who found this parasite in 7 per cent. of children in Paddington Green Hospital, the youngest being three months old. (f) G. Penso, in Italy, has divided the cases of this infection into three types: (1) non intestinal, associated with anæmia and nervous disorders, (2) intestinal with signs of enterocolitis, and (3) acute, with dysenteric symptoms. In the acute stage, when active stages are present, the stool is definitely dysenteric in character. (g) R. Deschiens (1923) believes that this parasite is pathogenic to children in France. C. M. Wenyon, in his review of this subject, concludes that it is difficult to avoid the impression that the mucus in the stools is produced from that part of the intestine where the flagellates are the most numerous, and is the result of irritation set up by their presence. He suggests that possibly certain individuals are more susceptible than others, and that the attacks of diarrhoea correspond with periods of active multiplication of this parasite.

With these latter views the author has been in agreement for a number of years, and he has had the opportunity of studying twenty six cases in adults in hospital. Most of the patients were admitted with a history of recurrent dysenteric attacks, and some, on account of the large, pale, ochreous stools they were passing, were suspected of sprue.

Arguments against the pathogenicity of this parasite are based

largely upon the very considerable number encountered who, with numerous cysts in their faeces, do not complain of intestinal symptoms.

It is a disturbing fact that *Giardia* is capable of multiplying in the human intestine without appearing either in the active phase or in cystic form in the excreta. Thus J McGrath, P T O'Farrell, and S J Boland (1939) have reported a case in which symptoms suggesting idiopathic steatorrhoea rapidly progressing to death, became apparent after cholecystectomy. The duodenal contents contained numbers of active *Giardia intestinalis* but, in spite of intensive search, none of the flagellates or their cysts were seen in the faeces. At autopsy the mucous membrane of the duodenum and jejunum was attenuated, the villi denuded of surface epithelium and in ulcerated areas of the jejunum and ileum large numbers of *Giardia*, which had penetrated the villi and crypts of the intestinal mucosa, were demonstrated. Somewhat similar fatal cases have been reported by Romano, Eusterman and Bonanno. The author in 1932 had under his care a case of amoebic dysentery with active and cystic forms of *I. histolytica* in the faeces. The fractional test meal showed achilorrhoea with no response to histamine, but in the fasting gastric juice numbers of active *Giardia* were present. The patient had previously undergone appendicectomy, cholecystectomy and gastrojejunostomy with short circuit operation. No active *Giardia* or cysts were ever found in the faeces. The patient was re-examined two years afterwards with the same results.

**Incidence**—In the author's series there were twenty-four cases in men and two in women. No infections in European children from the tropics were observed, though undoubtedly they do occur.

**Symptomatology**—The duration of the symptoms varies from one month to over ten years. The main complaint is of initial diarrhoea of a henteric character, followed by a more or less chronic condition of intestinal disturbance. Flatulence is almost invariably present. Acute exacerbations occur with diarrhoea and passage of a considerable quantity of bile-stained mucus.

The frequency with which the different symptoms were noted in the author's series was as follows: flatulence in fifteen, abdominal distension in four, lassitude in twenty-two, anorexia in eighteen, vomiting in one, alternate constipation and diarrhoea in twenty-four, chronic constipation in two. *Abdominal pain* varied in intensity from griping and a gnawing feeling in the epigastrium to mere discomfort. In one case only the pain appeared to be localized (to the umbilical region), in the remainder it was generalized. *Tenderness* on palpation was complained of in twenty-one cases: localized in the epigastrium in fifteen, in the hypogastrium in one, over the caecum in one, generalized in three, and was more pronounced during the night than the day. In nine cases the large bowel was spastic and palpable, especially the sigmoid colon, but in these there was a previous history of dysentery of the amoebic type. In three there was an associated enlargement of the liver.

*Stools* varied in number from two to eight per diem. The dejecta were pale or yellow, but, as a general rule, even more offensive than sprue stools, which they otherwise resemble. Usually they were of normal size. This description agrees in the main with the findings of other observers (S. A. Parodi and F. L. Nino (1926)). Most patients describe the passage of stools as being a matter of urgency, and several describe the nature of the action as being 'explosive'. In nineteen cases cysts of *G. intestinalis* were present in large numbers, and in two those of *Entamoeba histolytica* were also present. In only four cases were free and encysted forms of *Giardia* associated.

*Previous alimentary illnesses*—Eight cases in this series had a previous history of amœbic, and five of bacillary dysentery. Three had previously suffered from typhoid, and in two chronic indigestion, thought to be due to peptic ulcer, had been present for years.

*Associated illnesses*—In two cases there was coincident infection with *E. histolytica*, two also exhibited symptoms resembling those of sprue, and in another two, renal calculus was present, in one there was a coincident infection with *Ascaris lumbricoides*, and in another with subtertian malaria.

The following is a description of a typical case of giardiasis mimicking sprue—

A Government official aged fifty four, from Nyasaland, was seen in March, 1933, having been invalided home as a suspected case of sprue. Diarrhœa with the passage of light coloured matter and mucus, consisting of three to four stools a day, had been present for five months. There had been some loss of weight and considerable meteorism and discomfort, but no soreness of the tongue. The stools were light coloured, pasty, and fragmentary, and contained large numbers of active *Giardia* and cysts. Analysis of the faeces did not show a high fat content (fatty acids 9.8 per cent, neutral fat 4.4 per cent, total fat 14.2 per cent), and the blood calcium was 10.8 mgm. per cent. There was slight secondary anæmia. A barium enema showed no abnormality of the colon. The condition soon subsided on a meat dietary, combined with bowel lavage with 2 per cent sodium bicarbonate and quinoxyl. The patient has been examined since and has remained in good health.

*Giardiasis in children*—P. Veghelyi (1938) finds that infection by this parasite in children is symptomless or causes insignificant complaints in only one quarter of cases. In the majority, infection is followed by acute symptoms which may become chronic and lead to anæmia, which in turn impedes normal development. All these symptoms may be explained by impeded resorption capacity of the intestinal tract. The following complaints have been noted: anorexia, headache, diarrhœa and indefinite abdominal pains.

*Diagnosis*.—All the author's cases were examined by the sigmoidoscope, but there were no appearances in the large bowel which could be described as characteristic. Diagnosis is usually effected by the discovery of the parasite or its cysts in the faeces (Fig. 49).

*Treatment*.—The treatment of giardiasis was unsatisfactory before

1937, but the specific action of atabrin or quinacrine, as foreshadowed by L. Brumpt (1937) which banishes both the active parasite and its cysts from the faeces has been confirmed from a number of French (German, Russian, Italian Spanish and South American sources (A list of references is provided in the bibliography) Atabrin acts equally well when given by the mouth or injected in a soluble preparation atabrin musonate

The course consists of 0.1 grm. three times daily for 5-7 days. For children of ten years or more 2 tablets daily, one at midday, the other at night for 4-5 days (Garin and Vaffi) P. Martin (1937) considers

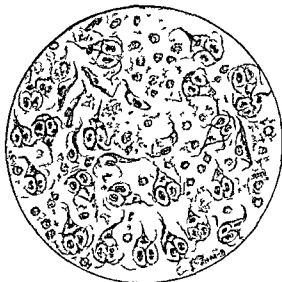


Fig. 49 —Mucous exudate in a case of giardiasis showing active flagellates disposed like fish in a stream

that it may be necessary to repeat the course. E. Votrna in a series of 25 cases finds atabrin effective in children especially when there are symptoms of enterocolitis but less so when there are associated symptoms of cholecystitis

J. Love and G. B. Tayloe (1940) have had remarkable results in four cases in which symptoms and parasites disappeared after a single course of atabrin. The author has verified these experiences in a series of seven cases under his care. In a recent communication J. T. Culbertson (1941) has confirmed that these parasites can be easily eliminated from man as well as from albino rats and mice by atabrin. Infections are permanently cured and relapses have not been observed. Acriflavine is equally effective but neither has any effect upon other intestinal parasites.

German and Scandinavian workers write enthusiastically about *Icranil*, the hydrochlorate of a new acridine compound, in doses of 0.5 grm, the dosage varying from 0.25 grm daily in children under 2, to 1.5 grm daily for 5 days in persons over 10. The results are said to be superior even to those obtained with atabrin, and the drug is less toxic (P. de Muro and F. W. Grott).

### FLAGELLATE DIARRHŒA\*

For some considerable time it has been questionable whether all the species of flagellates which have been described in the intestines of man are to be regarded merely as harmless commensals, or whether, on the other hand, they may be either primarily or partially pathogenic. The question does not admit easy solution. It cannot even be settled by deciding whether any individual flagellate (e.g., *Trichomonas*) is capable of invading the tissues or of ingesting red blood corpuscles. When associated with acute, subacute, or chronic diarrhœa, it is difficult to determine whether their presence is cause or effect. The presence of large numbers of these flagellates in the bowel content is probably due, to a great extent, to the fact that they thrive in a fluid medium, and that, when this becomes abnormal, as in bacillary dysentery, an environment is produced in which they can readily multiply. When, however, a case of chronic diarrhœa is encountered in which large numbers of active flagellates are lashing in the liquid fæces and no other obvious signs can be found, it becomes a question whether or not a pathogenic rôle should be assigned to these seemingly obvious agents of disease. Whatever the merits, the term *flagellate diarrhœa*, or *flagellate dysentery*, has come into use.

The presence of flagellates in the stools and the intestines certainly indicates faecal contamination of food taken by the mouth, and suggests that local sanitation must be defective. Therefore a high degree of flagellate parasitism indicates exposure to an abnormal degree of intestinal infection. This may account for the presence of *Trichomonas* and *Chilomastix* in large numbers in the fæces of severe cases of chronic bacillary dysentery and of sprue, and it should suggest to the clinician that there may be at the same time some other primary exciting cause of diarrhœa, such as amœbiasis.

It has been pointed out that the number of persons in whom intestinal flagellates are found is greatly in excess of those in whom diarrhœic or dysenteric symptoms are observed, that is to say, the majority of people infected exhibit no symptoms of disease, this suggests that the relationship of the organism to its host is one of commensalism. On the other hand there are those, for example, H. E. Whittingham (1923), who believe that flagellate dysentery is a definitely pathogenic condition, and that the parasites occur more frequently in the bowels of the unhealthy.

One cogent point in favour of those who hold that flagellates can

\* For a description of the morphology of the intestinal flagellates, see Appendix (p. 542).



cause a diarrhoea *suu generis* is that, after appropriate treatment such as colonic lavage, the active forms disappear from the faeces when the active symptoms subside, and when the faeces again become formed cysts of these parasites (i.e., *Chilomastix*) appear.

The majority regard *Trichomonas* and *Chilomastix* as distinctly non-pathogenic. *Trichomonas* has been found in the human mouth as well as in the vagina, but in the former situation there is no proof that it exists otherwise than as a saprophyte. This parasite has also been found in the male urethra and is not uncommonly found in the urine and, according to Liston (1940) it is capable of penetrating the epithelial cells lining the urethra. In gynaecological circles *T. vaginalis* is now regarded as the cause of irritative vaginitis and leucorrhoea. *T. fetus* is the cause of a similar condition in cattle, producing abortion. Special measures, such as stovarsol "vaginal compound S.V.C.", eliminate the infection. The vagina is douched with normal saline and two tablets inserted into the vagina for twelve days. This organism cannot survive at pH4. C. M. Wenyon (1920) has examined sections post mortem from five cases infected with *Trichomonas* and in one of these the organisms were found in the lumen of the intestinal glands, actually invading the cells, and distributed throughout the connective tissue. In the guinea pig there is a closely allied species which definitely causes ulceration of the intestinal mucous membrane. C. Dobell is doubtful whether all these trichomonads are in fact distinct entities, because he has been able to establish *T. intestinalis* in the monkey vagina.

Whittingham goes so far as to correlate neurasthenia with intestinal infection with flagellates. He sustains his hypothesis by pointing out that there is a chronic and unremitting irritation of the intestinal mucosa—an irritation which causes overaction of the cells and probably also absorption of toxic products from these organisms. Thus, stimuli are provided which, transmitted through the sympathetic system cause serious loss of nervous energy, ending eventually in neurasthenia. The vaso motor symptoms, such as lassitude, giddiness, and irritability, are thought to be part and parcel of this complex. Neurasthenia, however, is by no means confined to those infected by intestinal flagellates being also observed with amoebic dysentery and other forms of bowel disease.

Many observers, including H. M. Woodcock (1917), have seen *Trichomonas* ingesting red blood corpuscles but this is, possibly, not a normal happening. Others, for example, K. Tsuchiya (1925), in a detailed study of twenty cases heavily infected with *Trichomonas*, conclude that the organism is a harmless inhabitant of the large intestine, and that, whether numerous or scanty, it does not cause disease. On the other hand, W. E. Musgrave (1922) believed that *Chilomastix* may cause diarrhoea.

**Summary**—The author believes that the presence of *Trichomonas*, *Embadomonas*, *Chilomastix*, and other flagellates in the human bowel in

large numbers and in an active free state, in association with diarrhoea and dysenteric symptoms, indicates an abnormal condition of the mucous membrane of the large intestine which has previously undergone subacute or chronic inflammation. Furthermore, he believes the normal physiological processes of the goblet cells to be perverted, resulting in the production of an abnormally large amount of mucus, in which the organisms are able to obtain nutriment and in which they can multiply. This pathological state of the mucous membrane is primarily of bacterial origin, and usually indicates a previous infection with one or other of the dysentery bacilli. A bowel damaged by dysenteric toxins takes a considerable time to recover, during which period it acts in an abnormal fashion. A heavy infection of the flagellates, engrafted upon such a pathological condition, probably acts as an irritant, and tends to maintain this abnormal state. The flagellates must, therefore, be looked upon as secondary invaders, and means must be taken to eradicate them, if possible.

Additional evidence of their association with dysentery is afforded by the fact that, in chronic diarrhoeas of indigenous origin occurring in Europe where bacillary infections are very exceptional, flagellate diarrhoea is not usually met, whereas it is a very common state in those tropical countries where these bacillary infections abound.

**Treatment**—There does not appear to be any specific treatment for these infections as such, but the organisms disappear after vigorous lavage of the intestinal canal by irrigations of 2 per cent sodium bicarbonate, or by any other reagents employed as described on p. 103.

Stovarsol, 4 grains, or spirocid in similar dosage, two tablets daily for 8–10 days, has been reported by several observers to exert specific action upon *Trichomonas intestinalis*. Neither atabrin, acramil, nor acriflavine have any influence upon any intestinal flagellates other than *Giardia intestinalis*.

## INTESTINAL COCCIDIOSIS

Three species of coccidia, in the cystic stage, have been found in the faeces of man. Two of these have been found to be merely accidental, namely *Eimeria clupearum* and *E. sardinae*, which are parasitic in the genitalia of herrings and sardines and which pass through the human intestinal canal unchanged.

There is one authentic parasite of man, *Isospora hominis*, originally described by R. Virchow (1860) in the villi of the small intestine, and by T. Eimer in 1870 in two autopsies in Berlin. In 1915 Woodcock discovered the cysts of *Isospora* in the faeces of man, confirmed later in the same year by C. M. Wenyon.

The main interest in the case recorded by A. Connal (1922) was the unintentional infection of the investigator himself with the cysts of this coccidium. After an incubation period of six days, he suffered from diarrhoea, and in the evacuations the typical cysts were demon-

strated. The faeces were liquid, brownish yellow and contained incompletely digested material. No blood or pus cells were observed, but Charcot Leyden crystals were numerous. The outstanding feature of the faeces was the large amount of undigested material, especially fat. The oocysts persisted for thirty six days, after which they vanished and the patient recovered. Signs and symptoms, which were neither prominent nor severe, consisted of diarrhoea, abdominal discomfort, some flatulence, loss of weight, and a certain degree of lassitude. Treatment consisted in the administration of bismuth salicylate and charcoal three times daily.

**Ætiology.**—*Isospora hominis* (Raillet and Lucet, 1901), also known as *Isospora belli* (Wenyon, 1923), is probably a parasite of the epithelial cells of the small intestine, and it is likely that in this situation the full development will eventually be discovered. The oocysts vary in length from 25–33  $\mu$  and are almost half as wide as they are long. When found in the freshly passed human faeces they are transparent and colourless. An account from the zoological aspects is given in the Appendix (p. 548).

The most exhaustive and detailed account of the infection is by T. B. Magath (1935) who gives a list of 129 references in the literature.

The infection is undoubtedly world wide. *Isospora* has been observed now in the faeces of 203 patients distributed as follows —

Gallipoli	29	West Indies (author's cases)	2
Egypt	30	Johannesburg	2
Macedonia	26	West Africa	2
Iraq	20	Portuguese East Africa	1
Eastern Mediterranean	33	South Africa	1
Italy	2	Senegal	1
Syria	2	North China	3
Turkey	1	Wuchang (China)	1
North Africa	1	Bengal	4
Persia	3	Indo-China	6
Southern Russia	5	Philippine Islands	2
Uruguay	1	Dutch East Indies	6
Argentina	3	Hawaii	1
Brazil	8	U.S.A.	13

It will be observed that 75 per cent. of the recorded cases come from the Near East and the eastern Mediterranean area, these date from the 1914–18 war. In 1932 the first case in America was found by Magath in the Mayo Clinic, in a patient from Honolulu with diarrhoea. The extreme rarity of the infection is shown by the fact that this is the only authentic case in over 60,000 very carefully conducted stool examinations undertaken in that Institution.

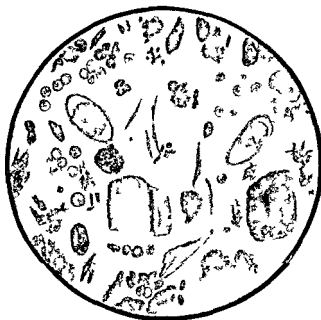
It is worthy of note that a mild form of diarrhoea with light coloured fatty stools, consisting to a great extent of undigested material, is described by almost everyone who has written on this subject, as is also the almost invariable association with numerous and large Charcot-Leyden crystals.

B M Das Gupta has shown that the cysts when scanty can best be demonstrated by the Willis flotation technique employed for ancylostome ova

In F Noc's case (1920) *Isospora* was associated with cysts of *Giardia* in E Reichenow's (1925) with cysts of *E. histolytica* ancylostome ova and a coincident infection with subtertian malaria and in the case described by Smyly and Kuie (1936) with cysts of *E. coli* and *E. nana*

H Gaillard (1936) found in Saigon a pure infection of *Isospora* in a child of two years of age who was suffering from acute diarrhoea. On the fifth day the patient died and at autopsy the whole intestinal tract was minutely examined without any lesion being detected. A number of others have been recorded in Europeans in Indo China by R Pons Dufossé and A Ieger. C Corcuff (1936) has reported two cases from Morocco associated with diarrhoea and Charcot Leyden crystals. C M Ter Matevossian and A T Tsaturian (1938) found a child of five suffering from diarrhoea of fourteen days duration in the Caucasus and *Isospora* parasites were numerous in the faeces

Two cases of *Isospora* infection both from South America have come under the author's notice during recent years. As it has been the invariable practice to make a microscopic examination of the faeces in every case the small number may be taken as a further indication of the comparative rarity of this infection (Fig 50)



P H M B

Fig 50—Cysts of *Isospora hominis* with Charcot Leyden crystals in the faeces.

The case of a commercial traveller was investigated in December, 1933. He had been touring round the West Indies, Bahamas, and British Guiana, and had become infected with *Isospora*. There was little doubt that the symptoms were definitely due to this infection. The syndrome was singularly similar to that described by Connal. The patient had suffered from chronic diarrhoea for over a month, with three or four motions daily, unaccompanied by pain or colic, and with but slight epigastric distress. There had been a definite loss of weight, and he looked depressed and ill. The faeces were light coloured and sprue like, and contained an excess of fat and undigested material. Charcot Leyden crystals were present in large numbers together with *Isospora* cysts and pus cells. A feature was the high eosinophilia (38 per cent) but no evidence of helminthic infection was forthcoming.

Treatment consisted of large doses of bismuth salicylate together with enemata of 2 per cent sodium bicarbonate. The cysts were seen for a further three days after which they disappeared. An opportunity presented itself of re-examining this patient two years later, when the faeces were proved to be normal.

The second was that of an explorer who had contracted amœbic dysentery in 1932 on the Amazon, and symptoms had persisted for two years. When he was examined the familiar signs and symptoms of intestinal amœbiasis were present so that it was difficult to assign any pathogenic role to *Isospora*. In addition to the cysts of the coccidium, those of *Entamoeba histolytica* and *E. coli* and subtertian malaria parasites were present in the blood. A high proportion of fat was found in the excreta. Sigmoidoscopic examination revealed nothing abnormal. This patient was re-examined three and a half years later and the faeces were then quite normal.

From this survey it is permissible to conclude that *Isospora hominis* is pathogenic for man and probably completes its schizogonic development within the mucous membrane of the intestinal villi. The symptoms it produces are those of a subacute dysentery, with the passage of light coloured faeces containing much undigested material, an excess of fat, and a number of Charcot Leyden crystals.

### MALARIAL DYSENTERY

Gastro intestinal disturbances are frequently observed in severe cases of subtertian malaria (*Plasmodium falciparum*). Severe diarrhoea, unaccompanied by fever and often ending fatally which in its intensity and rapid course, resembles true cholera, has since the days of Bignami, been recognized as the algid form of abdominal malaria. Such cases, with severe abdominal complications were noted in Salonica and Palestine during the concluding stages of the 1914-18 War.

The choleraic symptoms may develop unaccompanied by rigor or any of the more familiar signs of subacute malaria, or they may follow on an acute attack. The stools suddenly become profuse, numerous and choleraic, or they may be mucoid with admixture of blood. On two occasions the author demonstrated the ring forms of the subtertian parasite in film preparations of the faecal exudate. Usually the faecal matter retains a certain amount of bilary colouring but it may be colourless. As in cholera, the dehydration consequent upon the

diarrhoea may lead to cramps, pinched features, washerwoman's fingers, suppression of urine, and collapse. Such attacks are deceptive and may readily lead to a mistaken diagnosis. Where there is any reasonable doubt a thick film and thin film blood examination for malaria parasites should be performed as a routine, when trophozoites of *P. falciparum* are usually revealed.

Very often the spleen may be enlarged, but this is by no means invariable. Although the nose and extremities may be algid and the temperature subnormal, axillary and rectal temperatures will be found raised.

Sometimes dysenteric symptoms are present, with the passage of blood and mucus. They may be accompanied by hæmatemesis or hæmorrhage from the bowel, and in these cases it is difficult to decide whether the dysenteric syndrome is brought about solely by malaria or whether there is also an associated infection with bacillary dysentery. In fact, in malaria cases terminal infections of bacillary and amœbic dysentery were occasionally encountered during the 1914-18 War. This was also noted by L. Dudgeon and C. Clarke in Salonica, while D. Graham (1918) frequently isolated dysentery bacilli from malaria cases with dysenteric symptoms.

**Pathology**—Bignami first described punctate hæmorrhages in the mucosa. The vessels of the stomach wall and the large and small intestines are found to be packed with the sporulating parasites and there is widespread necrosis of the mucosa. Similar changes have been recorded by C. W. Daniels (1901) and R. Ross (1902) as well as by Marchiafava, C. Seyfarth, E. Job and L. Hitzmann and others. The following changes have been described: (a) intense infection of the mucosal vessels with parasitized cells, (b) necrosis of the epithelium, (c) leucocytic infiltration of the tissues subjacent to the necrotic zones and (d) invasion of the necrosed tissues with bacteria.

In his series of cases C. F. Craig described similar changes and even ulceration of the mucosa. The intestinal canal was found to contain blood stained mucus shortly after death.

**Diagnosis by sigmoidoscopy**—F. M. Arafa has described the sigmoidoscopic appearances of malarial dysentery as being characteristic. There is a diffuse hyperæmia and swelling of the mucosa, not unlike the appearance of the early stages of bacillary dysentery. The superficial necrosis is indicated by the appearance of greyish or yellowish white patches on the surface of the gut. When they are swabbed with cotton wool or are scraped, a congested and superficially ulcerated area is left. Arafa made preparations from the ulcerated surface, which show large numbers of degenerated endothelial cells and red blood corpuscles, and on one occasion he was able to confirm the diagnosis by finding a subtertian malaria gametocyte (crescent) in the exudate.

Further evidence of the correctness of the diagnosis can be obtained

by observing through the sigmoidoscope the healing of the intestinal lesions following anti-malarial treatment

*Summary of Cases of Malarial Dysentery seen during the 1914-1918 War* —  
 17/x/17 Private soldier seen after eating dates and other fruit. Violent diarrhoea and bloody vomit. Was first considered to be a case of colocynth poisoning. Admitted to hospital collapsed and almost pulseless. Mucous, bloody stools, consisting of gelatinous bright red mucus resembling those of acute bacillary dysentery. No enlargement of spleen. Microscopically, exudate in stools consisted of red blood cells, intestinal epithelium, and few pus cells. Stool plated out for dysentery bacilli, but only *B. coli* and *B. acidilactici* isolated.

After quiescent interval symptoms recurred with rigor and temperature of 104° F. Numerous subtertian malaria rings in peripheral blood and in stained preparations of the exudate in the stools. Quinine (25 grains) given intramuscularly with great improvement.

30/x/17 Private soldier, who had just been transferred from Salonica to Palestine. Sudden onset, acute diarrhoea with abdominal pain and sweating, no enlargement of spleen. Stool consisted of bright red blood and mucus. Microscopic examination, red blood cells abundant, with hæmatoidin crystals. Tongue dirty, icteric facies. Blood examination showed numerous rings and crescents of subtertian malaria. Sudden death four hours after. At autopsy, liver and spleen greatly engorged and tense and of greyish colour, grey discoloration of pancreas. Dense injection of intestinal capillaries. Rose red congestion and oedema of intestinal mucosa with hæmorrhages, especially in transverse and sigmoid colon. Overwhelming infection with sporulating subtertian parasites demonstrated in all organs.

12/xii/17 Private soldier. Abdominal malaria with choleraic symptoms and collapse. Gangrene of feet. Admitted with small running pulse, intense pallor, choleraic diarrhoea with incontinence, sunken, navicular abdomen, no enlargement of spleen. Dry tongue, sores on lips, icteric sclerotics, stools incessant, choleraic, offensive. Purple discoloration and icy coldness of extremities. Blood examination, large numbers of subtertian rings and sporulating forms. Death after intravenous injection of 7 grains of quinine.

*At autopsy*, great enlargement of tense grey liver and spleen, the latter spherical and swollen like miniature football. Great injection of intestinal capillaries. Rose red discoloration and oedema of intestinal mucosa. All vessels choked with sporulating subtertian parasites.

The following tragic history emphasizes the necessity of recognizing the gastro-intestinal symptoms as indicative of a severe subtertian malaria infection which may eventually end in coma —

A man of fine physique who had travelled far in the Middle and Far East for the previous twenty five years, paid a visit to the Gold Coast for the first time, and stayed there six weeks. He left Accra in perfect health but, though a "good sailor," experienced an attack of diarrhoea and vomiting on board ship, which commenced when two days out and became progressively worse, so that he was only able to retain small quantities of orange juice. He had no fever, the case was not diagnosed as malaria, and the gastro-intestinal upset was not considered serious. Liquid choleraic diarrhoea continued unchecked. He took no quinine on board ship.

On arrival he felt weak and shivering, but walked off the boat and came to London by train. That evening he was still vomiting, and was therefore given rectal saline and glucose. Next morning his condition was

serious and he had a rigor. A blood film showed an overwhelming infection with subtertian malaria, though the spleen was not palpable. After admission to hospital, he rapidly became unconscious, with cerebral symptoms, and he died in coma, not alleviated by intensive intravenous quinine therapy, on the following day. The cerebro spinal fluid was under considerable pressure. All the organs of the body, including the meninges, the brain, spleen, liver, and intestinal walls contained sporulating subtertian parasites, and in peripheral blood films melanophagy and phagocytosis of sporulating parasites were observed.

**Treatment.**—All cases of enteritis occurring in association with subtertian malaria should be treated seriously. It is probably best to commence treatment by intramuscular injections of quinine bihydrochloride (7–10 grains). In more urgent cases it may be necessary to inject the same amount intravenously. Thereafter, if the patient is able to retain it, anti malaria treatment should be continued with atabrin, one tablet three times daily after meals for seven consecutive days.

It is sometimes necessary to reinforce the atabrin treatment with small doses of quinine hydrochloride (5–10 grains) taken by the mouth. To check the diarrhoea a bismuth and magnesia mixture together with opium, should be employed. Should the diarrhoea continue in spite of these measures, gentle lavage of the bowel with normal saline or 2 per cent sodium bicarbonate, is advisable.

### LEISHMANIAL DYSENTERY

It has long been recognized that in patients succumbing to kala azar in whom a generalized infection with the parasite *Leishmania donovani* is present, ulceration of the small and large intestines is not uncommonly found, leishman bodies being demonstrated in the bases of the ulcers as a terminal complication. R. Jemma and G. di Cristina, in their cases of infantile kala azar in Sicily, noted the constant presence of entero colitis associated with circular ulcers in the large intestine. The two cases described by H. M. Perry (1922) merit special consideration.

In these the jejunum appeared thickened without any ulceration, and each villus was transformed into a swollen distorted and polypoid body. The columnar epithelium covering the villi had disappeared, and the basement membrane formed a limiting sheath for each swelling. The internal structure of the villi was completely altered owing to an intense proliferation of the endothelial cells lining the lymph channels. The distribution of Leishman Donovan bodies in the intestine was striking. They could be demonstrated in scanty numbers in the submucous coat, and in that position occurred in the endothelial cells derived from vascular endothelium. They were also present in larger numbers, in the same intracellular situation in the base of the villi, but in their centres rapid multiplication had taken place. (Fig 51.)

This peculiar pathology led Perry to speculate upon the possibility of escape of viable parasites *via* the intestinal canal. In dysenteric faeces so often passed by kala azar patients in the terminal stages of



the disease parasites have been demonstrated. T. P. Mackie (1914) found bodies resembling *Leishmania* in the smears of stools of patients in whom dysenteric like symptoms had been induced by the administration of croton oil while in one case of Mediterranean infantile kala azar A. Critch found them in the faeces, but H. E. Shortt, R. O. A. Smith, H. A. de Silva and C. S. Swaminath (1929) were really the first to



Fig. 51.—Microscopic section of the large intestine in kala azar.

I Arrangement of the Leishman-Donovan bodies in the neutral cells II and III, the bodies as seen under a higher magnification.

demonstrate these parasites consistently in the stools of kala azar dysentery with bacillary dysentery characters. There was much blood and mucus and films showed *Leishmania* in the exudate on two successive days.

In the artificially infected hamster H. E. Veleney has found similar changes in the gastro-intestinal tract the submucosa being filled by parasitized macrophage cells.

These findings have been employed as an argument in favour of the faecal transmission of kala azar and though this route has been found to be feasible under experimental conditions yet it is doubtful whether it occurs under natural conditions. Shortt, Smith and Swaminath succeeded in producing infection in one hamster which had been fed during a period of 467 days and on 160 occasions with faeces from kala azar patients.

## **The Helminthic Dysenteries**

## CHAPTER XVII

### BILHARZIAL DYSENTERY, ŒSOPHAGOSTOMIASIS, HETEROPHYIASIS, FASCIOLOPSIASIS, AND STRONGYLOIDIASIS

#### BILHARZIAL DYSENTERY

**Synonym.**—Schistosomiasis

**Definition.**—This is a group of diseases caused by three species of flukes or trematodes, belonging to the genus *Bilharzia*,\* which live in the venous system of man. There they produce large numbers of eggs which are extruded through various organs of the body, especially the bladder and bowel. Considerable damage is caused to the mucous membrane, and there are pathological changes in the liver and other organs due to toxins excreted by the parasites and to irritation caused by eggs.

It is not proposed here to consider the minutiae concerning this interesting group of parasites, a brief account, however, will be given of the ways in which they affect the different organs of digestion, and of the genesis of dysenteric symptoms. The three species concerned are *Bilharzia mansoni*, *Bilharzia hæmatobia*, and *Bilharzia japonica*.

**Ætiology.**—The parasites are digenetic trematodes, varying in length from 9 mm (*B. japonica*) to 2 cm (*B. hæmatobia*). They are unisexual, the male being the stouter and shorter. The female is enclosed in a groove caused by ventral infolding of the sides of the body of the male, this groove being termed the gynæcophoric canal. Both sexes are provided with an oral and a ventral sucker. The cuticle of the female in all three species is smooth, but that of the male is tuberculated, especially on the dorsal surface, except in the case of *B. japonica*, both male and female of which are smooth and in this species the suckers are relatively bigger and stronger. The alimentary canal consists of an œsophagus which bifurcates, forming two main gut branches which unite, usually about the centre of the body, into a median trunk, the cæcum, which ends blindly. The situation of this bifurcation varies, and provides a means whereby the different species can be distinguished from each other. The reproductive system of the male consists of four to nine testes and a corresponding number of

\* Cobbold named the genus *Bilharzia* after its original discoverer, in 1854, and this name therefore, has priority over *Schistosoma*.

vasa efferentia opening into a seminal vesicle the number varying in the different species. The reproductive system of the female consists of an oval elongated ovary, from the posterior end of which arises the oviduct which on passing forward is joined by the vitelline duct. The yolk glands or vitellaria occupy the posterior part of the body. The shell gland opens into the oviduct which then becomes the uterus and the genital opening is situated medially just posterior to the ventral sucker.

The eggs vary in shape and structure in the three species (Figs 52-53)



Fig 52 — *B. haematobia* : eggs in smear made direct from rectum ( $\times 130$ )

(Photomicrograph of I. I. K. Griffith, Amer. Med. Hosp. & Coll. Egypt)

and measure in length from  $60\mu$  (*B. japonica*) to  $150\mu$  (*B. leontobia*) averaging  $60\mu$  in breadth. The egg is provided with a spine which in *B. mansoni* is placed laterally and in *B. haematobia* terminally. In *B. japonica* there is a rudimentary lateral spine in the form of a minute papilla or excrescence.

**Geographical distribution** — *B. mansoni* is distributed throughout the continent of Africa, being most abundant in Egypt, the Congo, French West Africa and Nigeria. It is also common in South America—in Brazil, Venezuela and Dutch Guiana—and in the Antilles, especially Antigua. In some of the West Indian Islands the local feral monkeys (*Cercopithecus*) are naturally infected. Probably the dissemination of this parasite to the New World was originally due to slaves from West Africa. *B. haematobia* is almost entirely confined to Africa, but endemic foci also exist in Cyprus, Portugal, Palestine, Arabia and Iraq. After

the South African War infection was imported into Perth Western Australia but has since died out. *B. japonica* occurs most commonly in China where its main habitat is the Yangtse valley. It is also found in southern Japan, Upper Burma and southern Philippines. Wherever it occurs it is a natural infection in cats, pigs, dogs and cattle which act as reservoirs of the infection to man. It can easily be transmitted to monkeys, rabbits and other laboratory animals.

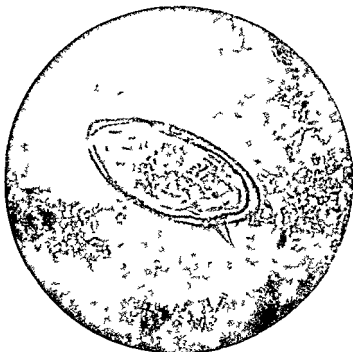


Fig 53—Lateral spined egg of *Bilharzia mansoni* in the faeces ( $\times 250$ )  
(Microphotograph D. Kerr)

**Life history**—The life history of these three parasites is in the main similar. Both sexes live in the venous system. The majority of *B. mansoni* and *B. japonica* are found in the portal and mesenteric veins and in the vicinity of the liver, but most *B. læmatobia* are found in the lower mesenteric branches of the portal, vesico-prostatic and pubic veins, the uterine plexus and the vesical veins. Occasionally they may wander into the vena cava and pulmonary veins.

The number of eggs laid by the different species varies. In *B. mansoni* usually only one or two are found in the uterus, the greatest number observed being six. In *B. læmatobia* twenty or thirty are present and in *B. japonica* fifty or more.

The method of deposition of the eggs is common to all three species. The female leaves the gynæcophoric canal of the male and by means

of the prehensile suckers enters veins, as her small size enables her to do. There she ejects an ovum from the genital opening situated just posterior to the ventral sucker. Usually the blunt, conical end of the egg is directed against the venous flow, while the posterior, bearing the spine, points in the direction of the blood current. The bilharzia then withdraws, and the venule contracts down upon the egg, holding it in position. Another egg is deposited as she withdraws further, and so on. Finally, when all the eggs have been deposited, the outline of the venule resembles a string of sausages (P. H. Manson-Bahr and N. H. Fairley, 1920).

When the female has withdrawn the blood current, flowing through the venule containing eggs forces the eggs through the coats of the vessel so that they gain the lumen of the bladder or intestine. Escape to the exterior is brought about by the mechanical passage of the egg through the tissues, aided by the penetrating action of the spine. In *B. mansoni* infection the greatest number of eggs are found in the colon, liver, and small intestine, *B. hæmatobia* are found in the pelvic viscera especially the bladder and uterus, though they may be found in the lungs even in the brain, but in small numbers in the spleen. Of *B. japonica* the greatest number of eggs aggregate in the walls of the intestines, mesenteric and retroperitoneal lymph glands, and the liver, occasionally in the lung but quite commonly in the brain. The bladder is unaffected.

The development of the three species in the intermediary is in the main similar. The egg coming into contact with water, hatches within ten to thirty minutes, the ciliated embryo (*miracidium*) escaping through a transverse rupture in the shell. This embryo swims about rapidly in a gyrating fashion, propelled by its cilia, for a maximum of twenty-four hours, after which it expires. The miracidium is provided with an anterior papilla or proboscis from which may be traced two salivary glands, but the greater part is occupied by germ cells.

The miracidia of the three different species are attracted by some peculiar influence (chemotaxis) to three distinct genera of fresh water snails. So specific is this attraction that they are drawn to these three, in which alone they can continue development. Boring through the antennae of the mollusc, the miracidium makes its way into the liver or digestive glands and becomes a *sporocyst*, in the interior of which daughter sporocysts form. These multiply to such an extent that the entire liver becomes permeated with long, delicate, tube-like bodies. The cells of the sporocysts become separated out into larval flukes or *cercariae* which possess distinctive structure and are composed of a body with a long bifid tail. It has been stated that there are minor differences in size and structure between the *cercariae* of the three different species. The caudal appendages enable the cercaria to swim about until it has gained its definitive host, and it can live in this manner for about twenty-four hours. It enters man by penetrating his skin, and in doing so the tail is discarded. Entering the lymphatics or blood

vessels, the immature flukes (*schistosomula*) proceed to the liver and the region of the portal vein, where in about six weeks they become differentiated into male and female bilharzia which soon produce characteristic eggs. According to the work of Japanese observers, the cercariæ derived from one particular snail develop into flukes of one sex, there are therefore male and female producing cercariæ. When once the flukes have attained maturity, it is probable that they can live many years, sometimes as many as thirty, their longevity being quite disproportionate to their size.

*Freshwater snails or intermediate hosts* — The following species have been found to harbour bilharzia —

INTERMEDIARY HOSTS FOR *B. MANSONI* —

Egypt	<i>Planorbis boissyi</i>
Tunis	<i>P. philippici sub-angulatus</i>
Sudan	<i>P. sudanicus</i>
Nyasaland	<i>P. neo sudanicus</i> , possibly <i>Melanoides tuberculata</i> (W. L. Gopsill)
Zanzibar	<i>P. gibbonsi</i>
South Africa	<i>P. pfeifferi</i>
Natal	<i>Physopsis africana</i>
Brazil	<i>Planorbis olivaceus</i>
Dutch Guiana	<i>P. olivaceus</i>
Central Brazil	<i>P. centimetralis</i>
North Brazil and Venezuela	<i>P. guadeloupensis</i>
	<i>P. glabratus</i>
Antigua	<i>P. guadeloupensis</i>
	<i>P. antiguensis</i>

INTERMEDIARY HOSTS FOR *B. HEMATOBIA* —

Egypt	<i>Bulinus contortus</i>
	<i>B. dybowskii</i>
	<i>B. innesi</i>
	<i>B. forskalii</i>
	<i>B. truncatus</i>
Palestine	<i>Physopsis globosa</i>
Sierra Leone	<i>Physopsis africana</i>
Natal	<i>Planorbis pfeifferi</i>
South Africa	<i>Planorbis pfeifferi</i>
Portugal	<i>Planorbis corneus</i> , var. <i>Metijensis</i>
Nyasaland	<i>Melania nodocincta</i> (Natal, rarely)
	<i>Lamnea natalensis</i>

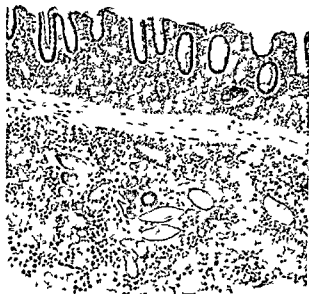
INTERMEDIARY HOSTS FOR *B. JAPONICA* —

South Japan and Central China	<i>Oncomelania nasophora</i> (Robson, 1915)
China	<i>Oncomelania hupensis</i>
Philippines	<i>Blanfordia quadras</i>
Formosa	<i>Oncomelania formosana</i>
Japan (Island of Sado)	<i>Blanfordia japonica</i>

It is not proposed to give a minute description of the above molluscs. The snails of the genus *Planorbis* are flat, Ammon horn shaped snails which float on the surface of the water, those of the genus *Bulinus*

and *Physopsis* are squat, spiral snails with an apical whorl and a sinistral opening, and those of the genus *Oncomelania* and *Blanfordia* are operculated long narrow spiral snails about 12 mm in length.

**Pathology of *Bilharzia mansoni* infection**—*B. mansoni* infection specially attacks the liver where, by deposition of eggs, a peculiar form of pipe stem cirrhosis is eventually produced. The passage of the eggs into the intestinal canal gives rise to a series of peculiar changes. The mechanism has already been described and the number of eggs in these tissues especially in colon and small intestine may be enormous. Dysenteric symptoms are produced in six to fourteen weeks from the



P. H. M. B.

Fig 54.—Microscopic section of the large intestine in intestinal bilharziasis showing eggs of *B. mansoni* and *B. haematobia* in situ

time of infection while focal lesions—polypi and adenopapillomata—are formed in from eight to fourteen weeks (Fig 54).

N. H. Fairley (1920) has studied the minute changes in the tissues in artificially infected monkeys and has found that in these animals the earlier pathological changes are due rather to toxins than to mechanical irritation and that a characteristic cellular humoral response is evoked. In monkeys death ensues from the second to the sixth week usually associated with intense melæna. The earliest localized lesions very closely resemble those of tuberculosis and are



known as pseudo tubercles. They are small whitish nodules varying in size from 0.5 to 4 mm in diameter, and consisting of fibroblastic cells with large numbers of eosinophils. Originally described in monkeys, they have now been confirmed in man by P. H. J. Lampe (1926) in Surinam, notably in the mesenteric glands, where they simulate tuberculous lesions closely. In that country 18.18 per cent. of autopsies show pathological changes due to this parasite. These pseudo tubercles are scattered throughout all the organs and especially on the peritoneal coats of the bowel. They may also occur on the intestinal mucosa, where they can be seen by the sigmoidoscope.

In addition to these pathological changes, deposits of black pigment granules (allied to melanin, probably hæmatin, a derivative of hæmoglobin) are found in the Kupffer cells of the liver. The mesenteric lymph glands and those of the retroperitoneal tissue are usually enlarged. The appendix may be affected, giving rise to bilharzial appendicitis. There is usually very distinct enlargement of the spleen, which is considered to be due not so much to the deposition of eggs as to toxic absorption. The splenic involvement has given rise to a distinctive disease known as Egyptian splenomegaly.

Affections of the colon may be divided into five types: (1) Those with simple thickening of the mucous membrane and the deposition of eggs in "sandy patches" in the mucosa, (2) thickening of the mucous membrane with papilloma formation, (3) pericolic tumours associated with papillomata, (4) polypi of the bowel, which may lead to intussusception, (5) cauliflower excrescences in the neighbourhood of the anus. One or all of these conditions may eventually undergo secondary malignant changes.

The presence of the eggs in the tissues can best be demonstrated according to A. R. Ferguson (1913), by digestion of the material in 3.5 per cent. solution of caustic potash at a temperature between 60° and 80° C. and subsequent centrifugation. By this means he showed that 61 per cent. of 600 male subjects in Egypt between the ages of five and sixty-five had intestinal infection with *B. mansoni*. It must not be thought that this is a purely intestinal infection; in a large proportion of cases in Egypt characteristic eggs can also be found in the urine.

Diffuse infiltration of the submucosa with eggs gives rise to a catarrhal and uniformly congested bowel. Usually there are scattered points of hæmorrhage without visible ulceration. When this process has lasted for some considerable time, the mucous membrane assumes a yellowish appearance due to the deposition of large numbers of eggs. It is this pathological state which gives rise to dysenteric symptoms.

*Formation of adeno papillomata*.—These small sessile and pedunculated growths are studded over the surface of the bowel, but, as a rule, are more numerous in the vicinity of the rectum. Sometimes they occur clustered in definite groups with healthy tracts of mucous membrane intervening, very often adeno papillomata co-exist with the diffuse deposition of the eggs already described (Fig. 55). As these

papillomata enlarge they often become elongated. They may be torn off by the peristaltic action of the intestines, thus causing sloughing, with formation of round clear cut ulcers. When these ulcers are numerous, and especially if they are secondarily infected, acute dysenteric symptoms are produced, with blood and pus in the stools. Sometimes, massive obstruction of the lumen of the bowel may lead to subacute intestinal obstruction. Papillomatous lesions of the stomach and ileum are extremely rare. The adeno papillomata of the bowel are usually associated with pericolic nodules.



P H M B

Fig 55 -Intestinal bilharziasis (*B. mansoni*), showing adeno papillomata in the rectum

**Liver**—In early stages of the infection the liver is slightly enlarged and is finely mottled and greyish in appearance. Internally it exhibits numerous minute dull white nodules, due to a degeneration of the liver cells produced by toxic necrosis. In the centre of these nodules eggs are present, usually singly or in groups, surrounded by a leucocytic zone consisting mostly of eosinophil cells. At a later stage it becomes somewhat reduced in size and the tissue is intersected by delicate fibrous strands, especially in the periportal zones. This cirrhosis is not sufficiently marked to produce pressure on bile ducts or veins, and secondary jaundice is absent. Immature bilharzia worms are found in the portal veins, and eggs are distributed throughout the liver.

The final expression of bilharzia disease is clay pipstern cirrhosis

The liver may be enlarged, although even in its extreme development this organ may not suffer any great diminution in volume. There is always a certain amount of perihepatitis, but the external surface is not "hob nailed" or strikingly irregular as in other forms of cirrhosis. The internal cirrhotic changes are more pronounced than would be inferred from inspection of the exterior. In all directions prominent islands and linear tracts of white connective tissue intersect the organ. At first it is quite vascular, and only in the later stages does it become dense and comparatively non vascular. The microscopical appearances in the early stages are those of a general cloudy swelling affecting the entire parenchyma, later on, when fibrosis has occurred, new duct formation takes place.

The pathology of *B japonica* infection is similar to that described

**Symptoms**—In the early stages toxic symptoms resembling those of the Katayama disease of *B japonica* are noted, especially in Europeans who have become heavily infected. The general signs consist of a high remittent fever with urticaria, marked abdominal pain, loss of appetite, rigors, and pulmonary symptoms. This stage, which may last six or eight weeks, was commonly seen in soldiers who became infected in Egypt in the early stages of the 1914-18 War. After the infection has lasted two months or more, symptoms become localized, with passage of dysenteric motions and there is little in general to differentiate them from mild attacks of amoebic dysentery.

In the terminal stages of the disease, large massive abdominal tumours may form, giving rise to discomfort and intestinal stasis, the liver becomes markedly cirrhotic, and ascites may be present. At this stage there is little to distinguish the clinical picture from that of other forms of ascites, indeed, hæmatemesis from rupture of distended œsophageal veins may take place.

Infiltration of the buttocks with eggs which have penetrated the tissues from the bowel is not uncommon, and leads to localized patches of induration and to fistula formation in the buttocks and in the rectum (Fig 56). Pneumonia and broncho pneumoniae manifestations are often observed in natives and are brought about by deposition of eggs in the lung tissue. At any stage acute dysenteric symptoms may supervene and may often be choleraic in character. These are the major manifestations of severe bilharzial disease. On the other hand, slight infections are extremely frequent and probably make up the greatest number of cases diagnosed. The eggs are then discovered accidentally in the laboratory while the faeces are being examined. They may be present in persons who have been exposed to infection on one or two occasions and whose general health remains good. It is most necessary, however, that all cases should be treated, because ultimately the disaster of cirrhosis of the liver is likely to take place. Symptomless cases are a danger, also as carriers of the disease.

A totally different clinical picture may be presented in visceral

infection known as *Egyptian splenomegaly*, a syndrome in which, some authorities hold, infection is by one sex of the worm only. This is a common disease in Egypt and Northern Nyasaland, possessing many features resembling kala azar. Anæmia, febrile disturbances, cirrhosis of the liver and ascites are the main features. It is endemic in Egypt, the Sudan, and Nyasaland, where 20 per cent of children under four years of age are found to be sufferers in various degrees. The hyperplasia of the spleen is, to a great extent, secondary to the hepatic cirrhosis, intestinal symptoms are usually absent and eggs of the parasite cannot be found in the stools. The fever is generally irregular of an intermittent type. The enlargement of the spleen



Fig. 56.—Rectal papillomata produced by eggs of *Bilharzia hæmatobia*  
(Dr H. K. Craig, Amer. Miss Hosp. Assut. Egypt.)

causes pain and discomfort, especially after meals, and gives rise to a dragging sensation on exertion. The final stages are ushered in by cirrhotic changes in the liver, which becomes progressively harder, and finally shrinks within the costal margin. The spleen also becomes fibrotic but does not proportionately decrease in size. Finally, the patient dies with symptoms of hepatic cirrhosis, ascites, and emaciation. Quite commonly, thrombosis of the portal vein takes place. Splenectomy, performed before the onset of ascites, has been successful. H. E. S. Steven (1928) has reported upon 390 cases, with a mortality rate of 13 per cent.

The blood picture varies in different stages of the disease. In the early stages there is a distinct leucocytosis of about 17,000, and myelo

cytes may be present, later, progressive microcytic anæmia becomes apparent and finally there is a leucopenia of about 3,000. There is usually a considerable increase in the eosinophil cells. The differential diagnosis from splenic anæmia is not always easy, in the latter there is usually a leucopenia with increase of lymphocytes, absence of eosinophils, and increase of blood platelets.

A parallel and similar splenomegaly occurs in *B japonica* infections and is known locally as "Katayama disease".

**Diagnosis**—The diagnosis of *B. mansoni* and *B. japonica* infection is made by the discovery of the characteristic eggs in the faeces under a microscope with low power. Usually they are very scanty, and it is necessary to examine several faecal films before arriving at a negative diagnosis. A concentration method which is very successful has been described by F. Fulleborn. A small quantity of faeces, the size of a hazel nut, is placed in a conical glass, carefully rubbed up with a glass rod in a few cubic centimetres of 2½ per cent salt solution, and put away to settle in the dark for five minutes. The solution is poured off the sediment and this process is repeated two or three times. The *Bilharzia* eggs remain in the sediment which is then mixed with distilled water at 120° F and exposed to a bright light. The miracidia immediately escape from the eggs and can easily be seen with a hand lens, particularly against a dark background. By adding a few drops of perchloride of mercury solution the miracidia are killed and can be found and recognized in the sediment.

Two other aids to diagnosis may be mentioned—the intradermal test of Fairley, which is performed with an antigen made from the cercariæ in the snail's liver, and the complement deviation reaction of the same worker. This is useful also in *B. hæmatobia* and *B. japonica* infections, and is positive in about 85 per cent of the cases. Sometimes when the blood serum is negative to this test in the advanced stages of the disease, ascitic fluid gives a positive reaction.

In cases of localized rectal disease, and especially where the masses resemble thrombosed piles, if *B. mansoni* or *B. japonica* be suspected, the adenomatous growths may be removed forcibly with forceps, crushed up in the saline solution, and examined under the microscope for eggs.

*Sigmoidoscopic examination* gives valuable information. A. G. Biggam and M. A. Arafa (1930) report that in the early stages small patches of granulation tissue can be observed at the bifurcation of blood vessels in the mucosa. In these hyperæmic areas typical small round, deep red spots, which are very characteristic of early bilharziasis, are seen dotted about on the surface of the mucosa. N. H. Fairley (1933) has also noticed small pale elevated tubercles, much resembling the "pseudotubercles" found in experimental bilharziasis in artificially infected monkeys. Later, polypoid localized thickening of the large intestine, and adenopapillomata may be recognized. Faeces may be removed from the rectum with the biopsy forceps and examined

under the microscope for cysts. Portions of papillomata when teased out in saline and examined may also reveal ova (Fig 57).

The papillomata may be either sessile or pedunculated and may be so massive as to obstruct the lumen of the bowel (Fig 58). Their colour is usually redder than that of the surrounding mucosa and sometimes actual hæmorrhages are seen. Seldom do lesions resemble the punched out depressed ulcerations of amœbiasis though sometimes both infections are associated. Treatment with intravenous injections of emetine and tartar emetic exerts no curative effect upon fully developed papillomata.



Fig 57—Lateral spined egg of *B. mansoni* in specimen obtained by sigmoidoscopy. Note that the shape of egg and size of spine differ materially from similar specimens seen in the faeces.

Palpation of the abdomen in the more advanced stages of the disease reveals a localized thickening of the large intestine usually due to pericolic growths which in the majority are situated in the transverse and pelvic colon.

*Differential diagnosis* is the same as for other forms of dysentery especially the amœbic form. As in other tropical diseases a very confusing situation occurs when more than one infection is present. In natives of Egypt a terminal infection with amœbic or bacillary dysentery is a common event in *B. mansoni* cases. It may be necessary to summon many aids to diagnosis in order to arrive at a correct conclusion. The cellular exudate in the stool resembles that of amœbic

dysentery, but the author has shown that eosinophil leucocytes are usually present in preponderating numbers. When pericolic masses are found in association with enlarged mesenteric glands especially in children the differential diagnosis from abdominal tuberculosis may be difficult.

**Treatment**—*B. mansoni*, *B. japonica* and *B. hæmatobia* infections are treated by intravenous injections of antimony thus killing the adult worms. The gross changes in the organs of the body are more severe in the two former infections because of toxic absorption. Intravenous injections of tartar emetic are given on alternate days commencing with

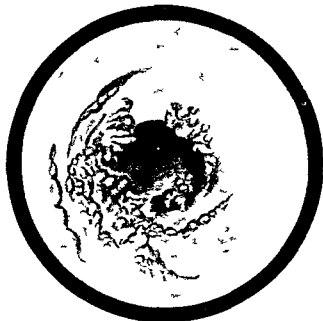


Fig. 58.—Sigmoidoscopic appearance of a case of bilharzial dysentery (*B. mansoni*) showing characteristic adenomatous papilloma.  
(After A. G. B. pyram.)

half a grain of tartar emetic (sodium antimony tartrate) dissolved in 10 c.c. of freshly-distilled sterile water. This amount is gradually increased half a grain at a time until the maximum individual dosage of 2 or 2½ grains is reached. Some authorities are in favour of dissolving the drug in a 5 per cent glucose solution as this neutralizes to some extent the toxic effects of the antimony.

In Egypt since 1925 the course consists of twelve injections three times weekly until 22½ grains have been injected this usually occupying about four weeks. When a small amount of diluting fluid is used as suggested above very few of the toxic symptoms due to antimony—such as headache, cough, nausea and transient

rheumatic pains—have been noticed P H J Lampe in Surinam (1926), has worked out a system for treating out patients with three injections of a 1 per cent solution of tartar emetic (8 c.c., 5 c.c. and 7 c.c.) during each week. A total of 25 to 30 grains is administered the course occupying six or seven weeks. A rectal injection of tartar emetic for young adults and children in whom for some reason or another, the intravenous route cannot be employed, has been worked out by Dye and others. A daily dose of 16 grains can be given by the rectum without producing toxic symptoms, but the exact amount of the drug absorbed is unknown. Five to seven daily treatments are necessary. Khalil has described a number of cases of bilharzial infection which appear to be antimony fast and he suggests that they are due to too rapid excretion in the urine.

The pentavalent preparations of antimony, by the intravenous route have not proved to be as efficient as in kala azar and other leishmania infections. Recently founadin (Bayer) has been used in Egypt by Khalil. This is a trivalent organic antimony compound, the formula of which can be expressed as antimony 3, pyrocatechin disulphonate of sodium. It is a white powder which contains 18.5 per cent of antimony. Nine to twelve injections of a 7 per cent solution given by the intramuscular route are said to be sufficient to cure the majority of cases. The following scheme has been advocated—

1st day	15 c.c.	11th day	5 c.c.
2nd day	8.5 c.c.	13th day	5 c.c.
3rd day	5 c.c.	15th day	5 c.c.
5th day	5 c.c.	17th day	5 c.c.
7th day	5 c.c.	19th day	5 c.c.
9th day	5 c.c.	21st day	5 c.c.

The drug causes little or no reaction and abscess formation and cellulitis, such as may happen with tartar emetic, are unknown. At present there is considerable doubt as to the permanency of the cure.

*Anthiomaline*, a new soluble lithium salt of antimony, has been favourably reported upon in recent years. It contains 16 per cent of antimony and is supplied in ampoules containing 2 c.c. each of a 6 per cent solution (or 0.02 grm. antimony). The dose for adults is 4 c.c., for children under twelve 0.5 c.c. Injections are made intravenously on alternate days, but are also tolerated by the intramuscular route. A total of 50 c.c. (0.5 grm. antimony) is necessary for an adult male in order to kill off both sexes of bilharzia worms. This preparation is said to be more toxic than founadin and may produce unpleasant though not necessarily serious symptoms.

*Emetine*—There is evidence, on clinical as well as the experimental grounds that emetine is toxic to the bilharzia worms. This was apparently known in Egypt before the discovery of the antimony tartrate treatment. The injection may be given intramuscularly to children who are intolerant of antimony tartrate or to those whose



veins are too narrow for intravenous injections. The initial dose is half a grain, the maximum single dose for a child being 1 grain, and a total of 15-20 grains may be given in all. The drug may be given to an adult, by the intravenous route, in doses of  $1\frac{1}{2}$  grains daily, the total course being ten injections, the average amount necessary is, according to H. Maciel (1924), about 0.6 grammes ( $9\frac{1}{4}$  grains).

Although it is not possible to influence, by means of drugs, the size or the development of the polypoid growths in the bowel, such growths may be dealt with by surgical means. R. V. Dolbey and Z. Fahmy recommended a method of removing them from the lower end of the rectum by excising a sleeve of mucous membrane. For this purpose a circular incision is made at the junction of the skin and anal mucosa, the external sphincter and levator ani attachments are separated by blunt dissections, and, when once the latter have been separated, a mucous tube may be loosened by the gloved finger and withdrawn until the upper limit of the papillomata is reached. Lengths of from 12-15 inches of the mucous membrane can be removed in this way. The lower part of the rectum is then left to granulate up. There is little tendency to retraction of the tube and control of the anal sphincter is soon regained. This type of operation is, however, quite unsuitable for very anæmic or debilitated persons.

Surgical treatment of the pericolic tumours in the abdomen presents a different problem. According to F. C. Madden (1919), these masses, however formidable in size, seldom cause intestinal obstruction. He states that in every case a simple laparotomy should be done, the thickened gut being incised and then sutured. In many cases this is followed by a considerable improvement in the distressing symptoms and by the apparent disappearance of the tumour itself.

In cases of bilharzial appendicitis in which the appendix is impregnated with masses of bilharzial eggs, removal is the only treatment. Surgical interference is also necessary for prolapse of bilharzial tumours through the anus, and bilharzial rectal fistulæ.

*Treatment of bilharzial splenomegaly*—These cases are nearly always associated with cirrhosis of the liver, and call for persistent tapping and withdrawal of ascitic fluid at frequent intervals—a wearisome process. Omentopexy has been tried but has not been very successful. Splenectomy has been undertaken by Owen Richards, Coleman and Bateman with considerable success. The latest reports show that a preliminary treatment for five or six weeks is necessary. This consists of a course of twelve tartar emetic injections together with carbon tetrachloride in those cases which are infected with ancylostomes, and with a full course of neosalvarsan in those complicated by syphilis. Immediately before the operation the patient should be given a rhubarb and soda mixture for one week, and then iron and arsenic to restore the blood. Stiven advocates, in addition, an injection of pneumococcic vaccine on the eve of the operation, to guard against pneumonia. Under the most favourable

conditions the minimum mortality is about 13 per cent. The average weight of the spleens removed by the aforementioned surgeons is 3½ lb. The favourable effects appear to be permanent and ascites does not develop later.

This, then, is a resumé of modern knowledge of *B. manson* infection in man. When the eggs of *B. hæmatobia* are found in the bowel, they apparently produce the same pathological effects. There are districts in Egypt and the Upper Congo where C. C. Chesterman (1933) has found in faeces elongated eggs resembling those of *B. hæmatobia*, and causing dysenteric symptoms similar to those already described. Some of these eggs are much larger than those commonly found in the urine and this has given rise to the speculation whether a distinct species of parasite, *B. intercalata*, which A. C. Fisher has described from Yakusu on the Congo may not be involved.

Another species of Bilharzia has been found in man in Southern Rhodesia by W. K. Blackie. This is known as *B. matthei*, normally a parasite of sheep and cattle, and has been demonstrated in the genito-urinary tract and in one instance, in the bowel. The eggs are much longer and more pointed than those of *B. hæmatobia*, and measure on an average 210-240 $\mu$  by 40-70 $\mu$ .

Little need be said about the treatment of the dysenteric symptoms produced by *B. japonica*. A larger amount of tartaric emetic is apparently necessary to overcome this infection. According to Faust and Meleney, 22-30 grains of intravenous tartar emetic over a period of 18-20 days are usually curative, but if the patient applies for treatment as he so often does when he is in the advanced stages of the disease when hepatic cirrhosis is well marked, then such treatment will have little effect.

## CEPHALOGASTROMIASIS

Cephalogastromiasis is a dysenteriform condition produced by a small nematode—in cephalogastrome—of which there are several species. The larvæ of this worm become encysted in the coats of the bowel usually in the large intestine, and gradually develop into immature cephalogastromes. They then rupture their cyst walls and pass into the lumen of the intestine or into the peritoneal canal where they become adult. The mammulated appearance of the mucosa closely resembles that produced by polypoids in man.

Anthropoid apes especially the orang outang certain species of monkey and some of the domestic animals can be infected by cephalogastromes. Weinberg has given a very complete report of the macroscopical and microscopical appearances of the disease in anthropoid apes and monkeys. It is a very rare disease in man. Brumpt reported the first case in 1905 in a negro from the Omo River, near Lake Rudolph in East Africa and Thomas the second from the

Amazon Autopsy in the latter case showed that the patient died of septic peritonitis due to the lesions caused by this worm

A man of thirty six years was admitted to hospital suffering from acute dysentery, he became delirious and died within three days

A metre of the surface of the small intestine, extending from the ileo cæcal valve, was studded with small, raised, dark coloured tumours, the majority of which were found in the lower part of the ileum within 35 cm of the ileo cæcal valve The nodules were less numerous and pronounced in the remaining 65 cm of the infected bowel Most of the growths were small and oval, they varied in size from that of a small pin's head to 7 x 9 mm and were elevated 6-8 mm above the surface of the bowel Some were flatter and button shaped, others were elongated leech like masses They were opaque and greyish black, with a few ochre coloured points in or beneath the cyst wall Many of the smaller nodules were hard and shot like, some were calcareous The tumours appeared to be firmly attached to the intestinal wall On examining the attachment of the ileum a worm was found penetrating the mesentery

The lesions were more extensive in the Brazilian case than in those cases described in monkeys by Weinberg The empty cysts can become cicatrized or calcified and the œsophagostome itself can produce hæmatotoxic substances analogous to those secreted by the sclerostome of the horse

R T Leiper has emphasized the fact that the nodules on the peritoneum look very like those of tuberculosis, and, being described as such, are often missed It may be, therefore, that œsophagostomiasis is a more common infection than has been supposed

**Ætiology.**—The species which was found by Thomas and described as *Œsophagostomum stephanostomum* (var *Thomasi*), differs only in minor details from the commoner species, *Œsophagostomum apistomum* The male is 17-22 mm in length by 0.77 mm in breadth The copulatory bursa possesses a dorsal ray which bifurcates, forming a horseshoe shaped structure, each limb of which gives off a short lateral horn near its base The female is 25-30 mm in length by 1 mm in breadth, ending posteriorly in a sharp point, and the vulva is situated near the anterior half of the body The eggs, 60 $\mu$  in length by 40 $\mu$  in breadth, which are passed in an advanced stage of development, closely resemble those of *Ancylostoma duodenale*

The life cycle appears to be as follows The larvæ, which hatch out of the eggs in the rhabditiform stage, are swallowed and pass undigested through the stomach and small intestine On arriving at the cæcum, they invade the wall and become mature, forming the nodules already described These worms are found both free and encysted in the wall of the large intestine The majority invade the cæcum

**Treatment.**—There are reasons for believing that phenothiazine, by mouth in tablet form (2-4 grm), is lethal to the œsophagostome The course is continued for 5-7 days On account of its toxic properties this drug is unsuitable for children

## HETEROPHYLIASIS

This is a small pyriform fluke found as a natural infection in the cat, dog, fox, and man. It is comparatively common in Egypt and the Far East, including Japan and Formosa.

The worm is very small, measuring only 1-1.7 mm in length by 0.8-0.4 mm in breadth, and it lives attached to the mucosa of the small intestine of the human host. The eggs are operculate, oval and light brown, measuring 28-30 $\mu$  by 15-17 $\mu$ . The miracidium, which escapes from the egg in water, develops in fresh water snails—*Melanoides tuberculata* and *Cleopatra bolumoides*. The cercaria is an oculate lophocercous larva, sometimes termed *Cercaria pleurolophocerca* (Sonstmo), which, on escaping from the snail, attacks the mullet (*Mugil cephalus*) or the minnow (*Gambusia affinis*). W. Khalil has recently traced out the development in quite a different snail, *Pirenella conica*, in Lake Manzala, Egypt. Infection of man takes place through consuming the raw flesh of the fish.

**Pathogenesis**—It has been reported by various observers that the presence of these small flukes in the intestine causes a catarrhal state of the bowel and consequent diarrhoea. G. Carmichael Low has cited one dysenteric case in which 500 adult trematodes were found in the faeces after the administration of eucalyptus, castor oil, and chloroform mixture.

## FASCIOLOPSIASIS

The term fasciolopsiasis denotes intestinal infection by the large leaf-like trematode, *Fasciolopsis buski*, an Asiatic species and the largest trematode which is parasitic in man. The average length is 80 mm, breadth 12 mm, and thickness 2 mm.

The evolution of this parasite and that of *F. hepatica* are in the main similar. The egg lies in water for two or three weeks and from it hatches a miracidium which enters and develops in the body of certain species of *Planorbis* snail. The cercariæ, escaping from the snail, encyst on the water caltrop and water chestnut which are freely eaten by the Chinese, forming a food known as *ling*.

**Pathogenesis and symptoms**—When a few *F. buski* inhabit the upper part of the small intestine they cause no inconvenience, but when many are present they cause diarrhoea with the passage of offensive stools. The first clinical signs come on about three months after exposure to infection. Grave symptoms simulating gastric ulcer, indicate the presence of large numbers of parasites. Oedema may be noted involving the face, abdominal wall, and lower extremities, ascites is common. In the terminal stages the skin becomes rough and dry and diarrhoea is continuous.

**Diagnosis**—Diagnosis is based upon finding the characteristic eggs in the faeces. The stools are greenish yellow and contain much undigested material.

**Treatment**—Beta naphthol, two treatments of 30 grains (2 grammes) each, and carbon tetrachloride (3 c.c. for an adult), are specific for this infection.

**Other trematode infections**—In addition to *Fasciolopsis buski*, the liver fluke (*Fasciola hepatica*) occurs, rarely, as an intestinal infection in man, and may give rise to similar symptoms. It is stated also that occasionally the eggs of the lung fluke (*Paragonimus westermani*) occur in the faeces, and give rise to dysenteric symptoms consisting of dull abdominal pains and occasionally diarrhoea. The differentiation from chronic appendicitis may sometimes be difficult.

### STRONGYLOIDIASIS

*Strongyloides stercoralis* (Bavay, 1876) is a small nematode which inhabits the small intestine, especially the ileum. It has a complicated life history, both within and without the human body.

The female parasite was considered to be parthenogenetic until the discovery of the male by H. A. Kreis in 1932. The females are colourless transparent, filiform worms measuring 2.2 mm. in length by 30–75  $\mu$  in diameter. They bore their way deeply into the epithelium of Lieberkuhn's glands where they deposit their eggs. The male is scarce and is shorter and broader than the female. It remains a lumen parasite, having lost its ability to penetrate tissue.

The embryos hatching from the eggs, appear in the faeces as rhabditiform larvæ, usually known as *Anguillula stercoralis*. A heterogenic development then takes place in soil and within thirty hours the larvæ have become sexually mature males and females—free living, unisexual adults. The females produce their eggs from which hatch infective filariform larvæ. It has been shown by Fulleborn that these parasites enter the skin and utilize the same route of invasion and migration through the human host as does the ancylostome.

**Pathogenesis and symptoms**—Ever since A. Normand, in 1877, discovered this species of nematode in the faeces in Cochui diarrhoea (sprue), it has been considered to be the cause of intestinal catarrh and diarrhoea. On entering the skin the infective larvæ may produce a localized dermatitis. When the intestinal mucosa is invaded a subacute catarrhal inflammation may be produced, giving rise to a diarrhoea with mucus and, it is said, the occasional appearance of occult blood.

There is considerable divergence of opinion as to the exact pathogenicity of this parasite. In the author's opinion it is quite harmless.

**Treatment**—E. C. Faust (1936) reports that gentian violet is an effective parasiticide in this infection when it reaches the living female in sufficient concentration. It is the only strongyloid therapeutic known and is given in enteric tablets in a dose of about 80 mgm. per kilo body weight, or, for the average adult male, 1 gr. three times daily for 7–10 days.

# The Infective Diarrhœas

## CHAPTER XVIII

### PARATYPHOID, TYPHOID AND FOOD-POISONING

**Definition**—The term 'food poisoning' should be restricted to acute gastro enteritis due to bacterial infection of food and drink. As employed here, it does not include "botulism," a disease which presents no symptoms of gastro enteritis.

The number of organisms recognized as capable of giving rise to food poisoning has greatly increased since the isolation of *B. enteritidis* by Gaertner in 1888, and it is now estimated that at least twenty seven members of the Salmonella group have been identified with actual outbreaks of food poisoning in human beings. It is not always easy to decide whether the train of morbid symptoms is brought about by the activities of the organisms themselves, or by the products which they elaborate. Nevertheless, food poisoning may conveniently be divided into two groups: (1) due to ingestion of pathogenic bacteria present in the food—the infection type, and (2) due to ingestion of certain substances, products of bacterial multiplication in the food before ingestion—or the toxin type.

In the *infection group* of food poisoning, after a short incubation period varying from a few hours up to three days, but usually within twenty four hours, the illness commences with headache, nausea, diarrhoea, and abdominal pains. There is, as a rule, a considerable degree of pyrexia and the temperature may rise to 102° F. In cases running a favourable course the symptoms gradually abate so that the patient recovers within a week, but in very severe cases there is restlessness which is followed usually by cramps, coma, and death. At autopsy the mucosa of stomach and intestines is found to be swollen and congested, Peyer's patches are not involved, though minute ulcers may be seen. There is usually fatty degeneration of the liver, and the causative organisms can be recovered from the blood, spleen, and other viscera. In the type of food poisoning caused by *toxins*, the general symptoms resemble those of the infection type, but the incubation period tends to be shorter—it may be half an hour to four hours—and vomiting more violent, prostration is greater, but there is less fever, so that recovery is more rapid. Fatal results are rare.

**Ætiology.**—The term 'ptomaine poisoning' has not been much used in scientific medicine since the discovery that many outbreaks were due to the organisms of the Salmonella group.

It has been shown, by the work of G. M. Dack, O. Jordan and others in Chicago, that certain strains of staphylococci are able to form toxic substances endowed with a degree of thermostability, affording proof of the formation of bacterial toxins in the food before its consumption. In 1935 E. O. Jordan and W. Burrows found that *B. typhi murium*

(*B. aertrycke*), given suitable conditions, may produce substances causing gastro intestinal irritation and there is evidence that members of the *Salmonella* group contain thermostable toxic substances which are soluble in water and are precipitated by alcohol. The method of extracting these bodies has been described by H. Raistrick and W. W. C. Topley (1934), who have proved that they are polysaccharides and, when injected into rabbits, cause fatal symptoms.

Recently, however, there has been a revival of the ptomaine theory, since it has been found that the multiplication in foodstuffs of many organisms not in themselves strictly pathogenic, such as *B. coli*, *Proteus vulgaris* and *P. morgani*, results in the formation of toxic substances which cause gastro intestinal irritation.

The chief food poisoning organisms are *Bact. enteritidis* of Gaertner, which has been found in contaminated meat in Germany, and *Bact. typhi murium* (identical with *Bact. aertrycke*), mainly responsible for outbreaks of food poisoning in England. During the year 1934 *B. typhi murium* was responsible for twenty two out of forty three outbreaks and out of forty six in 1935 it was isolated twenty nine times. In 1937 evidence that *B. proteus vulgaris* can cause mild outbreaks of gastro enteritis was brought forward by J. D. A. Gray. During the last few years a number of other organisms have been incriminated. The most important are *Bact. cholerae* suis Var. *Kunzendorf*, *Bact. thompsoni* and others. It was shown by W. M. Scott (1938) that 80 per cent of the more severe outbreaks in England are due to *Salmonella* infections.

In *Salmonella* epidemics the food has generally been meat, sometimes fish, shell fish, or other protein such as eggs, vegetables, or cereals. Usually the meat has been made into pâtés, pies, jellies or sausages, processes which may involve imperfect cooking and liability to contamination. Usually the food has been recooked, and sometimes it has been prepared and allowed to stand before being eaten. It must be remembered that, as a rule, the food appears quite normal to inspection.

During recent years attention has been directed towards poisoning by eggs. Duck eggs may be infected with *Bact. typhi murium* during their formation in the oviduct. Cattle and pigs are susceptible to infection with various types of *Salmonella* organisms of the food poisoning group. J. D. A. Gray (1937) has reported an outbreak due to contaminated cockles.

The opportunities for contamination of sound meat during the course of preparation for food are numerous, though it is often difficult to determine the exact manner. The main sources are rats, mice and human carriers. Both rats and mice suffer naturally from infection with *Bact. typhi murium* and *Bact. enteritidis*. Out of 121 outbreaks investigated, Savage could find only 5 in which a human carrier appeared to be responsible for infection of the food.

The following are the organisms which have to be considered as possible causes of food poisoning —



## SALMONELLA GROUP.—

- (a) *Salmonella paratyphi*—*B paratyphosus* A
- (b) *Salmonella Schotmulleri*—*B paratyphosus* B
- (c) *Salmonella enteritidis*—*B enteritidis* (Gaertner)
- (d) *Salmonella suispestifer*—*B ærtrycke*
- " *cholerae suis*
- " *ærtrycke*            } identical
- " *typhi murium*       } —*B typhi murium*

## OTHER ORGANISMS —

*Bacterium sonnei*—*B dysenteriae* Sonne

*Proteus vulgaris*

The paratyphoid organisms may be important, especially in time of war. The *Salmonella* group is sometimes referred to as the 'food poisoning group,' but *B paratyphosus* B is not generally considered to cause outbreaks of acute gastro enteritis, while the clinical signs and symptoms to which it gives rise are practically identical with those of *B paratyphosus* A.

Some authorities place *B typhosus* as well as the paratyphoid organisms among the food poisoning agencies, but the enteric group (*typhosus*, *paratyphosus* A and *paratyphosus* B) differs from the true food poisoning group in that the incubation period is longer. The enteric group are not natural pathogens of animals such as mice and rats, and their transmission is confined ultimately to human carriers. The symptomatology, also, is somewhat different. The type of illness caused by the paratyphoid organisms is usually a septicæmia, very similar to that of typhoid, but ulcerations produced are not confined to the small intestine, as in *typhosus*, but may cause lesions of considerable extent in the colon. Thus with paratyphoid infections diarrhoea is comparatively common, and occasionally blood and mucus stools may ensue. For this reason paratyphoid infections may become confused with the dysentery group. During the Great War, especially in the Gallipoli outbreak in 1915 in which most of the infections were due to paratyphoid B, the initial symptoms were frequently dysenteric in nature, subsequently typical paratyphoid pyrexia ensued.

Of course it is possible, as the author has been able to demonstrate, for a double infection of *B paratyphosus* and *B shigæ* to be present, but there have been many cases in which the former was present in pure culture, and in which the pathological appearance of the extensive ulcers in the large intestine sufficed to account for the dysenteric symptoms.

**Symptoms of food-poisoning.**—The symptoms commence almost simultaneously among a number of food consumers, in large outbreaks every degree of severity of illness is present. The excreta of those suffering from the poison are infective and thus it is spread to others. There is usually an incubation period of three to thirty hours. The

onset is sudden, with abdominal pain, tenesmus, diarrhoea, nausea, and usually vomiting. Headache, cold sweats, shivering, and syncope are present. The initial symptoms are usually the most severe. The diarrhoea rarely lasts for more than five days. Continuous vomiting denotes serious prognosis. When improvement sets in it progresses rapidly.

The physical signs cannot be held to be very characteristic. The tongue may be remarkably clean, the abdomen is usually tender, but not rigid, the spleen is not enlarged, and there is no rash. There may be pyrexia with a temperature of 102° F, but many cases are apyrexial. The stools are liquid and offensive, and when they are very frequent are occasionally streaked with blood. Blood and mucus in mass in the faeces are rare.

The sequelae of food poisoning are few, they are usually confined to the large intestine, and take the outward form of persistent diarrhoea or obstinate constipation.

The mortality is usually low, varying from 1 to 8 per cent. In the Limerick outbreak described by McWeeney (1909), nine deaths occurred in seventy three cases, but in a small outbreak due to *B. aertrycke* in Halle, Germany, six out of seven cases were fatal.

**Diagnosis** is usually a fairly simple matter, established upon the simultaneous appearance of numerous cases. Specific diagnosis is made by the bacteriological examination of stools and serum agglutination tests with recognized strains. In large outbreaks many cases may give negative bacteriological results. Microscopic examination of the faeces may be entirely negative or clumps of pus cells and red blood corpuscles may be revealed. The differential diagnosis has to be made from the dysentery group and from the enteric fevers.\*

**Treatment.**—The first essentials are to provide warmth to counteract the collapse, and fluids by the mouth or intravenously to dilute the toxins. In the early stages large doses of aperients are indicated, of which castor oil ( $\frac{1}{2}$  ounce) is the most suitable. For collapse, stimulants such as small doses of brandy or injections of strychnine are indicated. The diet should be carefully regulated and for the first twenty four hours nothing but fluids should be permitted. The best drug treatment for the gastro intestinal condition is undoubtedly bismuth, e.g. bismuth salicylate (10–15 grams) three times daily. For the constipation which so frequently follows the attack, petrolagar or liquid paraffin (2–4 drachms) are indicated.

In the typhoid-paratyphoid group, besides the well accredited dietetic measures, attention must be drawn to the favourable results recently obtained by the application of mandelic acid (sodium mandelate) by J. Kleeberg (1941).

\* See also (p. 78). T. H. A. Clayton and J. W. Hunter have shown that under certain circumstances *Salmonella* bacillus may cause symptoms closely resembling food poisoning.

## CHAPTER XIX

### CHOLERA

**Synonym** - *Cholera Asiatica*

**Definition**—An acute, infectious, epidemic disease caused by Koch's cholera vibrio. It is characterized by sudden onset, purging and vomiting of colourless, watery material, muscular cramp, collapse, suppression of urine, and, very often, sudden death. The mortality is usually very high.

**History and geographical distribution**—Cholera is endemic over the greater part of India, and has probably been so especially in Lower Bengal, from the earliest times. From this focus it has spread periodically, in epidemic form, over the whole Peninsula.

There have been, during the course of the last century and a half a number of well defined epidemics which are known to have spread from this region. In 1817 cholera began to extend all over Asia travelling eastward as far as Japan southward to Mauritius and westward to Syria and the shores of the Caspian Sea. Reaching Astrakhan in 1825 it spread no further. In 1830 cholera first visited Europe and since that date there have been at least five epidemics—1848-51, 1851-5, 1870-3, 1884-6, and 1892-5. It is true that there have been minor outbreaks since that time, but they have remained very restricted in area. In the Balkan War of 1913 and in the course of the Great War, 1914-18, there were a number of epidemics in the Balkans and in Iraq, but the disease did not spread as an epidemic beyond the actual seat of war. In the epidemic of 1870-3, Great Britain was practically spared, but the infection crossed the Atlantic and by way of Jamaica and New Orleans entered the United States, where it raged for a time. It has been concluded from a study of these epidemics that cholera has reached Europe by three distinct routes, (1) *via* Afghanistan, Persia, the Caspian Sea and the Volga valley (2) *via* the Persian Gulf, Syria, Asia Minor, Turkey in Europe and the Mediterranean, and (3) *via* the Red Sea, Egypt and the Mediterranean.

China is particularly liable to cholera epidemics, and in 1902 there was an extensive one. It is found as far north as Shanghai. Some isolated regions, such as the Andaman Islands, Australia, New Zealand, the Pacific Islands, South Africa, and the West African Coast, have so far escaped.

Of all the cholera disseminating centres in India, Hurdwar appears to be the most important, for this is a great pilgrim centre, the majority

of pilgrims travelling there from the Punjab, by this means cholera spreads all over India. The disease is carried to Arabia again by means of the pilgrim traffic. In 1865 it was carried by sea from Bombay to Arabia and Mecca, and was then widely spread by the returning pilgrims—throughout Egypt, Syria, and the southern European ports, to the East African coast, to the head of the Persian Gulf and up the Euphrates valley.

**Epidemiology and endemology.**—Cholera follows the great routes of human intercourse and is conveyed from place to place chiefly by man—probably by this sole agency. In India ideal conditions are produced for its dissemination during the religious gatherings, when hundreds of thousands of human beings are collected together under highly insanitary conditions. Cholera appears never to travel faster than man, but in modern times, owing to the increased speed of locomotion and the increased amount of travel, epidemics advance more rapidly and pursue a more erratic course than they did eighty years ago.

The endemic prevalence in India is best illustrated by the average yearly number of deaths in different provinces during the decade 1898-1907. In Bengal and Behar, the average yearly cholera mortality was 207,118, that is, 2.59 per thousand, in Madras there were 56,809 deaths, or 1.6 per thousand, and in Bombay, 26,782 deaths or 1.43 per thousand. It has been shown in the Annual Reports of the League of Nations that the mortality in British India has shown a tendency to decline within during the last thirty eight years.

*Seasonal influence* is of considerable importance. From available data it has been found possible to forecast epidemics of cholera two to three months ahead. The influence of climatic conditions has been studied by correlating individual factors, e.g., rainfall, humidity, etc., with the incidence of cholera in India, and a definite relationship is now established. High relative humidity with high temperatures, accompanied by intermittent rains, has been found to form the most favourable atmosphere for its development.

In Lower Bengal and Calcutta, however, the relationship is of a different kind. Here cholera is present throughout the year, having a definite maximal incidence in the dry, hot months of March and June when the water supply is most deficient and contaminated and a minimal incidence in the rainy season, when the water level is high and water supplies thoroughly flushed out. In Madras and Burma, where the climate is more equable, there is but little seasonal variation, and in the North West the maximum incidence becomes gradually less with the diminishing rainfall. Sir Leonard Rogers believes that in India the condition necessary for the spread of cholera is an absolute humidity of over 0.4, but this does not appear to be necessary for the spread of the disease elsewhere.

Cholera is mainly a water borne disease, and the bacillus enters by the stomach, there have been numerous historic instances to

bear this out. It is generally agreed, however, that ingestion of the bacillus is not the only factor necessary in the production of the disease. Probably the state of health and degree of acidity of the gastric juice render some more susceptible to this infection than others.

There are two types of cholera outbreak—one occurring when the general water supply is contaminated, the other when such contamination is localized to certain wells or other sources. In the former type the onset is explosive, and cases occur almost simultaneously, with equal distribution in all parts of the area affected, disappearing with almost equal suddenness. In the Hamburg epidemic of 1892, which may be cited as an example, during a period of only two months, cholera attacked 17,000 persons out of a population of 600,000, causing 8,605 deaths. The water supply of Hamburg was then taken directly from the Elbe, that of the adjoining city of Altona, with a population of 140,000, by a method of sand filtration, although this water was taken from the river after it had received the sewage of Hamburg yet there were in Altona only 328 deaths—2.1 per thousand against 13.4 per thousand in the former.

To illustrate the second type of water transmission, the well known incident of the Broad Street pump may be cited. This was the first definitely proven instance of the connexion between the drinking of water and the onset of cholera. In 1854 it was noted that cholera was ten times more prevalent in Golden Square than in other parts of London and also that the number of cases increased in the neighbourhood of the Broad Street well. The employees of a factory where this well water was used became heavily infected, while an adjoining brewery, which had a well of its own, did not furnish a single case. A particularly striking instance was that of a lady living at Hampstead, a part of London then free of cholera who, having acquired a liking for the water from the Broad Street well, had a bottle of it supplied to her daily. She drank some of the water on August 31, 1854, became infected with cholera, and died the following day.

D Herelle has made the interesting suggestion that the amount of bacteriophage produced in the intestinal canal is a factor in the rise and fall of cholera epidemics. Those patients in whose stools no bacteriophage is present die of the disease, while those in whom the bacteriophage is abundant rapidly recover. It is claimed that it can also be demonstrated in contaminated well water.

**Ætiology.**—It has been said, and well said, too, that although you can eat cholera and drink it, yet you cannot catch it, and this dictum is borne out by the well known immunity, as long as they do not eat or drink in the wards, of nurses and orderlies in cholera hospitals. The importance of a pure water supply in reducing the incidence of cholera has been illustrated in many cities, especially London and Calcutta. It is thought that food, especially uncooked vegetables and milk diluted with impure water, plays an important part in its dissemination, flies may carry the infection to all kinds of food. It is thought, also, that soiled clothes may be a source of infection but they can only retain infectivity when damp, moisture being essential to the life of the cholera vibrio.

In India, E. D. W. Greig (1913) stored the rice water stools of ninety four patients in a dark cupboard at room temperature taking care to prevent evaporation and found the average life of the vibrio to be seven or eight days in cool and one or two days in hot weather, the longest survival being seventeen days. In water the vibrio retains life for a variable time. A. C. Houston in 1909 added cultures of the vibrio to raw river water, and found that 99.9 per cent of the organisms died within one week and none survived longer than two. Some waters such as those of the Jumna and the Ganges, appear to be unfavourable to the survival of the vibrio, and much depends upon purity. Thus in spring water the vibrios live for thirty days, in Berlin water for six or seven days and in cesspools for less than twenty four hours.

Patients who have recovered from cholera may continue to excrete the vibrio irregularly for weeks. As a rule 90 per cent become free from infection in fourteen days and 99 per cent within a month.

*The cholera vibrio*—The cholera vibrio, or comma bacillus was first discovered by Koch in Egypt in 1883 and confirmed in Calcutta in 1884. His observations have been abundantly confirmed since that date.

The comma bacillus is a minute organism 1.5 to 2  $\mu$  in length by 0.5 to 0.6  $\mu$  in diameter, that is about half the length and twice the thickness of the tubercle bacillus. As a general rule it is slightly coloured by appropriate staining. Flagella can be distinguished at either end sometimes one less frequently two, these may be of considerable length—one to five times that of the body of the bacillus—but owing to their extreme tenacity they are difficult to distinguish in microscopic preparations. They impart an active spirillum like movement. Some individual bacilli, when stained show darker portions at the ends or the centre which suggest spore formation. Often in cultures two or more become joined together forming a spiral body. The cholera vibrio is stained by watery solutions of fuchsin, or by Löffler's methylene blue and is easily decolorized by Gram.

It grows best in alkaline media at a temperature ranging from 30°–40° C, growth is arrested below 15° and above 42° C while at a temperature of over 50° the bacillus is killed. Growing well in all the ordinary culture media, especially in alkaline peptone water and on potato in milk it multiplies rapidly without curdling. Although it dies quickly in distilled water it survives longer if salt is added. On gelatine plates it grows readily as minute white colonies granular in consistency irregular in shape. A zone of liquefaction is formed round each colony which sinks into a small depression. In gelatine stab cultures the growth is more abundant near the surface but as growth proceeds along the needle track liquefaction results which extends to the side of the tube. In older cultures involution forms are common and the organism dies out altogether after five or six weeks. The vibrio does not liquify agar and on this medium the colonies retain their vitality much longer. On potato it forms a brownish film and in broth a scum on the surface.

As a rule the vibrio does not haemolyse blood which is added to the medium on which it grows such as agar after twenty four hours of incubation. This test is performed by adding various amounts from 1 c.c. downwards of a three days culture in alkaline broth to 1 c.c. of 5 per cent suspension of goat's corpuscles and then thoroughly mixing. After incubation for two

hours the tubes are placed on the ice chest overnight, and are read the next day. With a 1 per cent solution of sugars the cholera vibrio produces acid in glucose, mannite, saccharose, and maltose. The fermentation of lactose proceeds more slowly and takes two or three days.

When all the morphological appearances and cultural characters are taken together, the result is fairly distinctive, but since certain other vibrios, e.g., that of Finkler, behave in much the same manner, a mistake may easily be made. One characteristic reaction given by the true cholera vibrio is that known as the cholera red reaction (due to the presence of indol nitrite in the medium), in which a red colour is obtained by the addition of pure sulphuric acid or other mineral acid to a cholera culture in 1 per cent peptone solution. The true cholera vibrio may be further recognized by testing it against immune rabbit serum, which will agglutinate the organism up to a titre of 1:12,000. This is by far the most satisfactory method of identification. J. Taylor (1938) has summarized the view of bacteriologists in India that the cholera vibrio belongs to Group 'O' No. 1 of Gardner and Venkatraman, is a non-hæmolytic vibrio possessing 'H' antigenic fractions in common with *V. cholerae* or belonging to 'O' groups other than No. 1, it is found in both healthy persons and cholera patients.

The virulence of the cholera vibrio can be raised by passage through guinea pigs. Successive culturing in the peritoneal exudate of these animals is alternated with culture media growths and virulence thereby becomes enhanced. A fixed virus, the virulence of which cannot further be affected thereby, results and this formed the basis of Haffkine's cholera vaccine.

It is only comparatively recently that all doubts that the cholera vibrio is the genuine germ cause of cholera have been dispelled. On many occasions cultures of the cholera vibrio have been swallowed by way of experiment, but in one single instance only has true cholera been reproduced. It is thus probable that, for the production of the clinical condition known as cholera, other factors are necessary in addition to the vibrio. The disease can only be produced in lower animals by administering cholera cultures after lowering the general resistance—in ground squirrels by large doses of alkalis.

Inagglutinable vibrios known as paracholerae, such as Finkler Prior and El Tor, resemble the true cholera vibrio closely, and so, also, do organisms found in fowl cholera, in decomposing cheese, and in river water, but they behave entirely differently when tested out serologically, and they are now generally considered to be biologically distinct. Although a great deal of work has been done on the subject, and interest in it has recently been revived, the significance of these non-agglutinating vibrios still remains a matter of some doubt. J. W. Tomb and G. C. Maitra (1927) by employing what is known as the open bowl method of enriching cholera cultures in a cholera district, have been able to show that 35 per cent. of the inhabitants are chronic carriers of non-agglutinating vibrios. They consider that agglutinating vibrios are merely different phases of the same organism. They hold that agglutinability is an artificial property developed and fixed by laboratory cultivation, since laboratory cultures of vibrios take approximately three times as long to agglutinate as those in stools from which they are derived though all lose their agglutinability under artificial conditions. J. J. van Loghem has raised the whole question by pointing out that the true cholera vibrio is hæmodigestive, not hæmolytic, while the El Tor vibrio is both hæmodigestive and hæmolytic. W. Doorenbos regards the El Tor vibrio as a true cholera vibrio contaminated with bacteriophage.

**Toxins**—Filtered cultures of the cholera vibrio exert little poisonous action, the virus is apparently liberated by the breaking up of individual organisms and dead cultures, when administered by the mouth, produce little effect unless the intestinal canal is injured in some way. These poisonous bodies are mostly destroyed at 60° C., but, when ground up and frozen by liquid air, an extract is obtained which is extremely toxic if injected intravenously into laboratory animals.

**Immunity**—Most laboratory animals, especially the rabbit and the guinea pig, may easily be immunized against the cholera vibrio by repeated intra peritoneal injections of dead cultures, and the serum thus obtained possesses high agglutinating powers—up to 1:20,000. In tests for proving that the vibrios isolated from a given stool are those of true cholera, a serum should be employed which gives a titre of 1:4,000. Thus, when injected into non-immune animals, it exerts a protective power four or five times as great against the lethal dose of organisms. The active bacteriolysis which takes place is known as Pfeiffer's reaction. The test is performed as follows:—

A loopful of a young agar culture of the vibrio is added to 1 c.c. of broth containing 0.001 c.c. of anti cholera serum. This is injected into the peritoneal cavity of a young guinea pig and, by means of capillary tubes inserted into the peritoneum, the peritoneal fluid is examined microscopically every few minutes. Should the original culture be that of a true cholera vibrio, the organisms break up into small globules, if not, no change takes place. This is regarded as the surest proof that a suspected organism is true cholera.

**Pathology.**—The appearances found after death naturally vary considerably with the severity and duration of the disease. If death occurs in the *algid stage* of cholera, the surface of the body appears shrunken and wizened. Rigor mortis occurs early and persists for some time, and, owing to post mortem muscular contractions, movements of the limbs may take place. On opening the body all the tissues are found to be abnormally dry. The muscles are dark and rigid, and some may actually be found to be ruptured. The right side of the heart and all the main veins are distended with dark thick, imperfectly coagulated fluid, while fibrinous clots extending far into the vessels may be found in the right heart. The lungs, which are usually bloodless, dry, and contracted, may occasionally be congested and œdematous. The pulmonary arteries are distended with blood, while the corresponding veins may be empty. The liver, too, is generally congested, the gall bladder full of bile, and the spleen small and shrunken. No fluid is found in the peritoneal and pleural cavities. The bowel is congested and red, and on opening it a certain amount of the characteristic rice-water fluid is obtained. The mucous membrane of the stomach and intestines, either as a whole or in part, is congested and pink.

Should death occur during the *stage of reaction*, the tissues are moist, and less congestion of the venous system is observed. The lungs are congested and œdematous and there may be signs of an extensive enteritis. The intestinal contents may present evidence of bile, while Greig has shown that the cholera vibrio frequently enters the gall bladder, which may act as a reservoir of infection. Sometimes the vibrios may be demonstrated in the lungs, kidneys, or spleen and very occasionally



they may be found in the urine. They occur in large numbers in the stools in the acute stages of the disease, and in the contents of the intestines. Evidence of infection is most abundant in the upper part of the small intestine and duodenum, but may with difficulty be found in the large. In microscopical sections vibrios may be found lying between the epithelial cells of the villi.

*Cholera carriers*—The carrier state is now recognized as one of the most important factors in the spread of cholera, and it has been found that in some instances as many as 20 per cent. of those in immediate contact with a cholera patient may assume this state. Some may exhibit symptoms of disease, but the greater number maintain apparent good health. During a period when cholera was present in Manila, A. J. McLaughlin (1916) found 6–7 per cent. of carriers among healthy persons living in the infected districts, and Pottevin (1921) has reported that out of 13 000 pilgrims examined 17 per thousand were carriers of cholera vibrios, so that, he holds, possibly the carrier state lasts for two months or more. In the acute stages cholera vibrios are excreted by the patient for seven to ten days; more usually they disappear in three or four. Y. Y. Ying (1940) has found, however, that occasionally positive cultures may be obtained for four weeks. Generally speaking, cholera patients should be isolated for two weeks. If positive after that date they should be regarded as carriers.

*Symptoms*—Although the clinical picture of cholera may vary almost infinitely, yet there are certain outstanding manifestations. The cholera syndrome may supervene upon what appears to be an ordinary case of henteric diarrhoea, or it may come on suddenly, with full development of characteristic signs without any warning.

The difficulty about the clinical recognition of cholera is that diarrhoea of all kinds appear to be more prevalent during a cholera epidemic than at other times, and it is a matter of common observation that people who have any intestinal disturbance are more likely to be attacked by the disease than those who have not. In most cases the milder symptoms constitute the stage of premonitory diarrhoea and are known as cholerae. In some, premonitory symptoms take the form of languor, depression, noises in the ears, and disturbances of vision. The incubation period is short, where this has been accurately worked out as in the instances recorded by Macnamara (1918), it is within twenty-four to seventy-two hours from the time of infection.

The onset of true cholera is marked by the sudden evacuation of profuse watery stools, at first faecal in character, afterwards becoming colourless, like thin rice water containing small flocculi. Enormous quantities—it may be pints—are passed by the patient. At this time, or very soon afterwards, vomiting of food material, and later of the "rice water" liquid, supervenes. The patient is then attacked with painful cramps of the muscles of the limbs and abdomen, the unfortunate sufferer being agonized by these contractions, which cause the muscles to stand out like rigid bars. He then passes into a state of collapse.

Probably owing to dehydration through diarrhoea and vomiting, there is a general shrinkage of the softer tissues, the eyes become sunken, the cheeks fall in, the nose assumes a peculiarly thin, pinched and blue appearance; and the skin of the fingers becomes shrivelled like that of a washerwoman. The general temperature is lowered, and the body becomes cold, livid, and moistened by a cold, clammy sweat. Very soon the flow of both urine and bile is suppressed, and the respirations become shallow and rapid, the breath is cold and the voice reduced to a mere whisper. The circulatory system suffers severely and the pulse soon becomes feeble and thready and, after fluctuating, may disappear. Although the surface temperature of the body is much below normal (it may be as low as  $93^{\circ}$  or  $94^{\circ}$  F), that of the rectum may register from  $101^{\circ}$ – $105^{\circ}$ . Restlessness now sets in and the patient tosses about uneasily, throwing his arms from side to side and complaining of great thirst, of a hot, burning sensation inside his chest, and general cramps and aches in the limbs. All through this agonizing period, his mind generally remains clear, although in some instances it may wander and he may pass into a comatose condition. This is known as the '*algid stage of cholera*', and may terminate in death, in a general febrile reaction, or in rapid convalescence.

When death occurs, usually from collapse, it generally takes place within ten to twelve hours of the onset, the extremes are from two to thirty hours. Convalescence is ushered in by a gradual cessation of vomiting and diarrhoea, re-appearance of the pulse at the wrist and the return of warmth to the surface of the body. Soon, after apparent suppression for many hours, secretion of urine once more takes place, and in three days or more the patient may be practically well, without any complications. The relationship of anuria in cholera to that of collapse and crush injury, which possess the same physiological background, has recently been emphasized by J. W. Tomb (1942). Collapse of the circulation in cholera, as well as in traumatic shock, results from over stimulation of the sympathetic nervous system and causes dilatation of the capillaries of the skeletal muscles as well as constriction of those of the skin and abdomen.

Usually, however, what is known as the *stage of reaction* supervenes upon the *algid stage*. This is sometimes known as cholera typhoid. The signs of restoration of the circulatory functions become more evident. Recovery appears to set in with return of the pulse, increasing temperature of the skin, and re-appearance of urine, accompanied by diminution of the restlessness. At the same time diarrhoea is diminished and the stools contain more bile. At this stage a febrile condition of variable severity may suddenly develop. Minor degrees of this reaction may subside within a few hours, but in severer cases the febrile state becomes more and more aggravated and a fever resembling that of typhoid, cholera typhoid ensues. This febrile reaction is doubtless due to a renewed absorption of the toxins from the bowel, coinciding with revival of the circulation. It is during this

stage of reaction that death may take place from a variety of complications—pneumonia, enteritis, even asthenia—or, more commonly, from the effects of delayed uræmic poisoning

In a cholera epidemic, great variety in the character and severity of symptoms is observed, and generally the earlier cases show much more severe changes, while those towards the termination of the epidemic are usually milder

The mildest cases are known as cases of *ambulatory cholera*, and are characterized by malaise and diarrhœa. These patients never suffer from complete suppression of urine, the diarrhœa never loses its bilious character, and cramps do not occur. Such mild attacks subside without the reaction stage

*Cholera sicca* is a very fatal type. In these cases there may be no diarrhœa nor vomiting at all, but collapse sets in so rapidly that the patient, overwhelmed by the infection, dies within a few hours without purging or any attempt at reaction

*Hyperpyrexia* may very occasionally supervene, the temperature rising rapidly to 107° F in the axilla and to as high as 109° in the rectum. Such cases are almost invariably fatal

*Special features*—During the early days of the acute stage there is a definite increase in the number of red blood corpuscles, which may rise to 8,000,000 per c mm. At the same time there is an increase of leucocytes, according to L. Rogers (1923), an average of 28,000 per c mm is usually met, those cases with a specially high count being generally, but not always, fatal. In the differential count there is an increase in the proportion of polymorphonuclear cells, together with a great decrease in the lymphocytes. According to Rogers, the most characteristic feature is the loss of fluid from the blood. This has been ascertained by centrifuging defibrinated blood in the hæmatocrit, by which means the relative proportion of corpuscles to serum is ascertained. Rogers estimated that in the blood of an Indian there is normally 45 per cent of corpuscles to 55 per cent of serum but in cholera patients 71 per cent of corpuscles and only 29 per cent of serum were found, indicating a loss of nearly one half the fluid from the blood. After intravenous injections of hypertonic saline, the normal proportions are rapidly restored. Estimations of the amount of chlorides in the blood-serum in cholera show that salt is reduced to a greater proportion than is the fluid. The physiological results of this chloride loss are self evident

It is on the estimation of the *specific gravity of the blood* that the greatest diagnostic value is placed. In cholera the specific gravity is raised from the normal of 1,056–59 up to 1,063, the limit being about 1,065. The method of estimating the specific gravity was elaborated by Rogers from the Lloyd Jones glycerin method, and is as follows. A series of solutions of glycerin and water are made up at room temperature in specific gravities of from 1.040–70, each solution increasing in specific gravity by two units. Stock solutions are kept in a series of small stoppered bottles. The finger tip

being pricked a small quantity of blood is sucked up into a capillary glass tube and then blown into the selected gravity bottle. If it sinks it is heavier; if it rises it is lighter, and another drop is blown into another bottle until the medium is found in which it just floats. These observations take but a few minutes to make, but the data they furnish point the way to accurate treatment.

The *blood pressure* is also important in cholera and is greatly reduced in the collapse stage. In those cases in which the systolic blood pressure falls below 70 mm. of mercury, it is necessary to administer intravenous saline injections, in order to maintain the blood pressure and enable the kidneys to resume their normal functions.

**Sequelæ**—Cholera may be followed by a variety of sequelæ of more or less importance. There may be *anæmia*, physical and mental debility, *insomnia*, febrile conditions, chronic *nephritis*, various kinds of pneumonic consolidation of the lung, even *cholecystitis* resulting in jaundice. *Parotitis* occurs in about 1 per cent of cholera cases and usually ends in abscess formation. Eye complications are frequent and severe, for instance, ulceration of the cornea with sloughing may ensue after prolonged collapse in which the eyes are kept half open. Rapidly developing cataract has been seen. Bed sores are common and gangrene of the penis, scrotum, nose, mucous membrane of the mouth, toes and fingers has been recorded by older writers. Dysentery and diarrhœa may also follow true cholera, but eventually may clear up without much trouble. In elderly and enfeebled people a state of *asthenia* may develop. The danger of sudden cardiac failure must at all times be borne in mind. Pregnant women almost invariably miscarry, and the foetus shows evidence of cholera infection.

**Diagnosis**—The diagnosis of cholera on clinical grounds should not, during the height of an epidemic, be particularly difficult. There is the characteristic appearance of the patient, the cold, clammy fingers, the cyanosis, the feeble whisper, the shrivelled fingers and toes, the cold breath, the suppression of urine—all these are sufficiently distinctive. It is in the minor manifestations, the doubtful cases, and the carriers that scientific methods of diagnosis must be employed.

In true cholera the comma bacillus, or vibrio, may be recognized in the stools under the microscope, but it may not be found at the first examination.

The usual procedure is for the stools to be microscopically examined. If the vibrios are present in large numbers, they may be detected by their movement in a hanging drop preparation or by their characteristic appearance in films stained by carbol fuchsin. Koch considered that in 50 per cent of cases diagnosis could be made by this method. When the vibrios are numerous plates may be spread by means of a platinum loop on *Drigondé's* medium, the alkalinity of which possesses the property of preventing to a great extent the growth of organisms other than the cholera vibrio. The colonies may then be recognized by their characteristic appearances.

When the vibrios are present in small numbers, alkaline peptone water should be inoculated with one or more loopfuls of the fluid stool and incubated for seven hours. Any pellicle present on the surface of the broth should be examined in stained films or by the hanging drop method. If the vibrios are very scanty, they should be reinforced by inoculating a second alkaline peptone tube, incubating for a further six to eight hours and then plating out on alkaline agar. Finally an emulsion of the colonies from the plate or from the agar culture should be agglutinated against the specific antiserum in high titre. A positive agglutination of over one in a thousand with a specially prepared cholera serum is strongly suggestive of the true cholera vibrio.

To carry out the full procedure for the identification of the cholera vibrio as laid down by bacteriologists, a considerable amount of time is required, yet it is quite obvious to anyone who has studied the subject that promptness in recognizing early cases of the disease and in identifying carriers is of great importance. To meet this need for promptitude various rapid methods have been devised.

Bandis's method consists of inoculating the suspected faeces into peptone water containing the agglutinating serum in such a strength as to clump the cholera vibrios in high dilutions. After three hours' incubation agglutination which is visible to the naked eye will be observed, this is, however, rather a wasteful method, for when employed on a number of cases a large quantity of serum is used.

The author, in conjunction with A. Davies, employed a modification of this method in Palestine in 1917 and 1918 with apparently satisfactory results. The method consists of agglutinating the vibrio in peptone water cultures made from the stools, by small quantities of immune serum on the slide of a Garrow's agglutinator. By this method positive results may be obtained in as short a period as eighteen hours and as many as two hundred stools may be examined during the course of a morning. The following are the stages—

1. A platinum loop full of faeces is inoculated into peptone water (1 per cent peptone, 1 per cent sodium chloride made distinctly alkaline to litmus).

2. It is then incubated for eighteen hours.

3. A drop of the resulting growth is placed on the slab of Garrow's agglutinator, together with a drop of 1 in 80 anticholera serum (*See p. 565*). The resulting mixture will give a dilution of cholera serum of 1 in 160. On the next partition is placed an equal quantity of normal saline, together with a drop of the peptone culture to act as a control. The slab should then be rotated for three minutes. If the vibrios are present a definite agglutination will be obtained and this can be confirmed later by testing out with cholera serum in high dilutions.

4. The peptone culture can then be spread with a platinum loop on Crendropoulos agar (alkaline agar) and a pure culture obtained by this means. The cholera colonies can now be easily recognized by their transparent bluish grey appearance, and hæmolytic and sugar tests can be applied. These necessarily consume more time, and it has been found that vibrios in the cultures which are agglutinated with specific serum in higher dilutions invariably give the correct sugar, hæmolytic, and cholera red reactions.

To confirm the diagnosis at an autopsy on a suspected case of cholera two portions of the small bowel, about five inches in length, one just above the ileo-cæcal valve and the other in the middle of the ileum, should be ligatured cut off, dropped into sterile saline and sent to the bacteriological laboratory as soon as possible. The blood serum agglutination test is not a very satis-

factory method of making a diagnosis in true cholera, for an agglutination reaction is not obtainable in the blood serum during the acute stage of the disease it is present after eight to ten days from the commencement reaching its maximum in four weeks when it may attain a titre of 1 : 1000

**Differential diagnosis**—The conditions from which cholera has to be distinguished, and the main point of investigation in each case may be tabulated as follows —

*Symptoms referable to the gastro intestinal system*

Food poisoning	History of patient
Choleraic malaria	Blood examination for malaria
Acute bacillary dysentery	Cell exudate in stool
Acute arsenical and mercurial poisoning	History
Mushroom poisoning	History
Summer diarrhoea of children	Character of stool

*Symptoms referable to pains and cramps in limbs*

Fireman's cramp	History of patient
Trichiniasis	Leucocytosis and eosinophilia

In other forms of diarrhoea, it has been pointed out that it is rare for the stools to remain as persistently free from bile as they do in cholera. A careful inspection of the stools may yield useful information in other ways. In mushroom poisoning fragments of the fungus may be recognized and in acute trichiniasis the adult trichina may be identified by the microscope. In choleraic malarial attacks the spleen is enlarged and the subtertian parasite may be demonstrated in the blood stream.

True cholera has to be differentiated from ptomaine or food-poisoning which may simulate it very closely, but in food poisoning there is usually a history of several persons being attacked at much the same time after having eaten some article of food. It is said that a great point in the differential diagnosis is that a leucocytosis is present in the early stages of cholera, but absent in food poisoning. J W Tomb gives the following useful differential table between these two conditions

TABLE VIII

	CHOLERA	FOOD POISONING
Diarrhoea	Painless. Precedes vomiting	Associated with severe abdominal pain, generally follows vomiting
Vomiting	Causes no distress. Watery, copious and projectile. Follows diarrhoea	Often violent and distressing. Vomitus consists of food and is never watery copious or projectile. Generally precedes diarrhoea
Nausea	Absent	Constant
Tenesmus	Absent	Common

	CHOLERA	FOOD POISONING
Stools	Rice water and copious	Liquid but faecal and offensive Never colourless or copious
Urine	Complete suppression	Never suppressed
Muscular Cramps	Constant Severity depending on the amount of fluid lost from the tissues	Present only in very severe cases Often associated with tingling and numbness Mild and confined to the extremities
Collapse	Frequent, chiefly from loss of fluid	Never from loss of fluid In severe cases faintness or syn- cope may occur from toxæmia
Fever	Surface temperature below normal	Axillary temperature 99-102°, accompanied by shivering in severe cases
Headache	Absent	Frequent

*Mushroom poisoning* produces symptoms resembling food poisoning it is dealt with on p 478

*Algid or choleraic malaria* may simulate cholera very closely, and during the 1914-18 War the author saw many cases of this condition about which a scare of cholera had been raised amongst the troops (See p 268) Subtertian malarial attacks are often accompanied by choleraic symptoms, the stools suddenly become loose, profuse and numerous, but they are not nearly so copious as the rice water material which pours from the patient in true cholera The diagnosis is confirmed by means of a microscopical examination of the blood and discovery of the subtertian malarial parasite

*Acute bacillary dysentery* may be so sudden and severe in its onset as to resemble true cholera, and epidemics of the former disease have actually been officially mistaken for the latter (See p 60)

*Acute arsenical and mercurial poisoning* may also closely resemble cholera, but as a general rule vomiting is the most urgent symptom As in cholera, a leucocytosis may be produced with a high proportion of polymorphonuclears Generally in these cases a history of poisoning can be substantiated

*Fireman's or stoker's cramp* occurs in those employed under conditions of excessive heat and moisture, such as are found in the engine rooms and stokeholds of ships in the tropics, especially in the Red Sea The sufferers excrete frequent watery stools and suffer from marked collapse and severe muscular cramps, these cases thus bear a considerable resemblance to cholera The signs and symptoms are brought about through loss of chlorides by excessive sweating and treatment consists of giving large amounts of fluid by the mouth (sodium chloride, 2 drachms to the pint)

In acute *trichiniasis*, a disease which is fortunately becoming far less frequent, gastro intestinal irritation is produced at the stage when the adult worms in the small intestine reach sexual activity Abdominal pain, vomiting, and severe diarrhoea of the choleraic type may ensue,

with muscular cramps and pains. There is usually pyrexia with a leucocytosis and high eosinophilia. Supplementary measures are the intradermal and precipitin tests whenever they are available.

#### TREATMENT OF CHOLERA

The principles of treatment of cholera may be tabulated as follows —  
*Measures controlling efficacy of treatment*

Specific gravity of blood    blood pressure,    estimation of the urinary flow    body temperature

#### *Therapeutic measures*

Hypertonic saline    intravenous sodium bicarbonate, intestinal disinfectants, potassium permanganate    Tomb's essential oils, kaolin

During cholera epidemics it is most necessary that every case of diarrhoea should be efficiently treated and for this purpose it has been customary to establish small depots where sedative and astringent remedies are dispensed. Chlorodyne 15–20 drops twice daily, has been found to be of value in stopping the progress of the disease. In the early stages of true cholera diarrhoea, opium is of undoubted value and a hypodermic injection of morphia  $\frac{1}{4}$  grain together with atropine  $\frac{1}{100}$  grain should be given immediately. With the morphia, the following anti diarrhoeic mixture is of value —

R. Sod bicarb	15 gr
Cret prep	15 gr
Sp æther	15 m
Sp ammon aromat	15 m
Tinct opii	30 m
Aq chlorof ad	1 ℥

One fluid ounce of this should be given every twenty minutes until the vomiting or the diarrhoea ceases.

**Kaolin** —The exhibition at this stage of kaolin or bolus alba as an intestinal astringent which at the same time adsorbs the cholera toxins has many advocates. It was first used by Stumpf in the Serbian epidemic of 1912. Kaolin powder 100 grammes is put up in 250 c c of water to make a suspension and a glassful of this is sipped cold every hour or every half hour during the day but not more than six glassfuls or 200 grammes should be taken in the first twelve hours. It has been found inconvenient to give this on a large scale on account of the bulk of the dose.

**General measures** —The patient must be kept warm in a horizontal position in a well ventilated room. Thirst should be treated by sips of iced water or normal saline soda water champagne or brandy and water but copious draughts which are likely to provoke vomiting are usually contra indicated. The cramps may be relieved by gentle



massage with the hand or by rubbing in some liniment. Sometimes small injections of morphia are necessary; sometimes chloroform inhalations have to be resorted to. The body should be kept dry by wiping with dry cloths, and the surface heat should be maintained by hot water bottles placed about the feet, legs, and flanks. On no account should the patient be allowed to get up to pass his stools, and a warm bedpan should be provided for this purpose. The foot of the bed should be raised. It is necessary that all solid food should be withheld while cholera is active.

**Essential oils.**—A popular and well established method of routine treatment in India in village epidemics, where scientific methods are not readily available, consists of a mixture of essential oils containing aniseed, cajuput and juniper, which is made up as follows —

R. Sp. æther	30 m
Ol. anis	5 m
Ol. cajuput	5 m
Ol. junip	5 m
Acid. sulph. aromat	15 m

Of this, half a drachm is given in half an ounce of water every quarter of an hour. The average total dose should be 8 drachms. This mixture should be given immediately cholera symptoms are noticed, and J. W. Tomb has claimed that in 95 per cent. of cases recovery takes place within seven hours of the onset. Vomiting, purging, and intestinal distress appear to be immediately controlled.

**Rogers's treatment.**—As the stage of collapse in cholera is due to the loss of so large an amount of fluid from the body, intravenous injections of saline have been resorted to in order to restore the balance. In the milder cases, the injection of normal saline solution in sufficient quantities appears to act well, but three or four pints may be necessary. If the veins are difficult to find, the injection of saline may be made into the peritoneum or into the muscles of the breast. It is said that after a preliminary introduction of two to four pints of normal saline solution into the peritoneum, the superficial veins become prominent, and intravenous injections become practicable. Owing to their collapsed condition it is usually necessary to cut down on to the veins to insert the needle and cannula.

Rogers's treatment is based upon the physical conditions underlying the chief symptoms—the blood pressure, the specific gravity of the blood, and the loss of salt from the body. Already in 1893, A. J. Wall, considering the routine treatment of cholera by castor oil and calomel to be mischievous, advocated intravenous injection of 0.4 per cent. of sodium chloride and 0.2 per cent. of sodium bicarbonate dissolved in sterile boiling water. He made a practice of stopping the injection when the pulse was restored. In moderate cases this took place after the injection of 70 ounces, and in severe ones, after the injection of 5 pints.

Wall's methods were adopted and modified by Sir Leonard Rogers on the following lines —

1 The specific gravity of the blood should be estimated to determine the loss of fluid from the bowel, both as a guide to the necessity for administering the saline injection, and as a guide to the amount to be given. This estimation should be repeated regularly every morning and evening, and also whenever signs of collapse occur. A rise to 1032 is an indication for a saline injection, which, if given early, before actual collapse has taken place, will prevent the development of a serious condition.

2 The blood pressure should be estimated at the same time, since a fall to a dangerous degree, i.e., below 70 to 80 mm in Indians or 80 to 90 or 100 mm in adult Europeans, is an indication for a saline injection even if the specific gravity of the blood is not much reduced.

3 Hypertonic saline solution for intravenous injection is advocated to replace lost salts and to increase them to a little above the normal physiological point. This is done to retain the fluid in the blood vessels and to maintain the blood pressure and circulation, thereby leading to excretion of the toxins from the system.

4 A certain amount of alkali—bicarbonate of soda—is given with the salt solution as long as the urine is acid, to combat the tendency to acidosis which predisposes to suppression of urine.

5 An oxidizing agent, such as permanganate of potash, is administered freely by the mouth, to destroy the bacterial toxins which are being formed in the gastro intestinal tract.

6 The temperature should be carefully watched and controlled during the stage of reaction after returning circulation and renewed absorption of the intestinal toxins.

7 The blood pressure and the amount of urine being excreted should be watched and all available means employed to maintain the blood pressure at a level which will ensure free renal secretion.

It is probable that the more modern continuous-drip intravenous saline method holds out greater possibilities in the treatment of cholera.

*Temperature of the fluid* —It is necessary to pay very close attention to this point. Owing to the markedly subnormal temperature of the body in the collapsed stage, it is advisable to administer the saline solution several degrees above blood heat. According to Nichols and Andrews, the fluid in the containing needle should be at a temperature of at least 43° C (109.4° F), thus, allowing for the cooling which occurs while it runs through the tube, the temperature of the fluid on entering the veins will be from 4° to 6° F above blood heat. The low surface temperatures seen in cholera patients are largely due to deficient circulation, and this is instantly restored to normal by the intravenous injections of salines at blood heat. The hypertonic saline which is most favoured for this purpose is composed as follows —

B. Sod chlorid	120 gr
Pot chlorid	6 gr
Calc chlorid	4 gr
Sterilized water	1 pint

The rule now adopted is that the fluid in the containing bottle should be at temperature of 100° F. if the rectal temperature is below 99° F. If the

latter is above 100° F there is a risk of hyperpyrexia and the injection should be given at a temperature varying between 80° and 90° F

The solution is introduced by means of a special stopcock cannula and transfusion bulb at a rate of not more than 4 ounces a minute the flow being slowed down to 1 ounce a minute should distress or headache supervene

On an average, in the severe collapsed stage of cholera in an adult male, about 4 pints of fluid are required the rule laid down being with a specific gravity of 1063, 3 pints should be injected, of 1064, 4 pints, of 1065, 5 pints

With this intravenous medication, Rogers combined hypodermic injections of atropine, 1/100 grain, morning and evening

It is now becoming increasingly evident that rapid and lasting effects on the restoration of the circulatory equilibrium are more likely to be obtained by the physiological method of transfusion with plasma, or the more recently elaborated reconstituted plasma the latter is eminently suitable for the conditions in which cholera is usually found

**Permanganate of potash**—The routine administration of permanganate of potash has received a very considerable amount of support In cholera the alimentary tract is so completely cleared of its normal contents that any substance which has the power of destroying toxins readily comes into contact with the poisons formed in the bowel The permanganate treatment must be combined with intravenous salines to save a severely collapsed case The simplest plan is to give the patient permanganate solution to drink *ad libitum* in place of water, if he can retain it Owing to the intense thirst in the acute stage of cholera, there is usually no difficulty in inducing patients to swallow permanganate solutions in a strength of from 1 to 6 grains to the pint Failing this method, potassium permanganate is given in pill form up to 50 grains a day, 2 grains being given every quarter of an hour for two hours, and then every half hour until the stools are coloured green The pills are made up of finely powdered potassium permanganate, 2 grains, kaolin and vaseline, q s, and are coated with salol one part and sandarac varnish five parts, or with keratin It is essential that they should not be kept long, for they decompose

**Bacteriophage in the treatment of cholera**—In recent years attention has been given to the treatment of cholera by the specific choleraphage of d Herelle The results have not been very encouraging I N Asheshov, I Asheshov, Khan, and Lahiri (1933) have given it together with intravenous hypertonic saline, the fluid being sterilized under pressure in the autoclave, and not by boiling Usually however cholera bacteriophage is given undiluted by the mouth in 1 drachm doses every 30 minutes, or 5 c c are administered intravenously for more rapid action

That many of the claims made are uncritical is substantiated by the comprehensive review by J Taylor (1937), and by the records of analysis of figures at the Campbell Hospital, Calcutta which show no appreciable difference in the death rate of cases so treated and the controls Boulnois (1936) in a limited outbreak at Chandernagore where it was possible to administer choleraphage within 1 and 12 hours of the onset found no appreciable difference between those treated by bacteriophage alone and those receiving

combined treatment with hypertonic salines, but there was marked improvement in the subsequent incidence of cholera amongst contacts as compared with controls. S. K. Chatterjee and L. R. S. Dey (1938) assert that the bacteriophage must be of the quick acting type. Its administration must be in massive doses at the earliest opportunity. The dominant phage is of the A type which has a generation period of under one hour. It is this phage which can be separated in a large proportion of convalescents.

**Anticholera serum.**—B. Ghosh has published several papers on the use of a new anticholera serum with increased potency, made by a method of toxin production and prepared with the object of procuring a maximum quantity of both endo and exo toxin. This serum was tried out in forty seven cases of cholera in Calcutta, being given by the intraperitoneal route. The mortality rate compared with a series treated by other methods was 10.63:20.5. The serum treatment was reserved mainly for those cases in which the blood plasma had a specific gravity of 1.064 or over. Quantities of from 70 to 80 c.c. of concentrated serum were given only to patients with high toxæmia and a high specific gravity of the blood. Possibly the absorption of the serum by the peritoneum is not so rapid as has been supposed.

The intravenous route for injection of serum does not produce such favourable results.

**Treatment of the stage in which copious evacuations occur.**—The great majority of cases come under the care of the physician at this stage, and it may be taken as a principle that no drugs given by the mouth will be of any value in restoring the circulation, because they cannot be absorbed. Stimulant or astringent drugs become inert. There are several instances of this on record, Macpherson for example, has recorded the case of a native who swallowed 33 grains of opium and 55 drops of croton oil, yet recovered without a single symptom and without any further purging. In another instance, 22 grains of extract of belladonna, given by the mouth and by the rectum, produced no dilatation of the pupils.

Rogers considers that the great problem in cholera is to restore and maintain the circulation, and that, if this can be done, the toxin will be rapidly excreted through the kidneys and recovery will take place.

**Rectal injections of normal saline.**—These may be tried in comparatively mild cases, when the large bowel retains its powers of absorption. As long as there is a fair pulse, the patient may be tided over the danger of collapse by frequently-repeated and copious saline enemata. Observations have shown that, when the blood pressure remains above 70 mm., rectal injections, if retained, will be absorbed, absorption being shown by a rise in the blood pressure and a fall in the specific gravity of the blood. It is unsafe, apparently, to rely upon enemata beyond this, as, absorption being deficient, further copious evacuations may rapidly produce a dangerous degree of collapse. In all cases in which rectal salines are relied upon, close watch must be kept on the patient, especially on his pulse.

For rectal injections Rogers used 90 grains of sodium chloride to the pint, making a 0.95 per cent. solution or just about the concentra-

tion in which sodium chloride is found in the blood in mild cases of cholera. As long as the urine is acid—and it usually is in the acute stage of cholera—160 grains of sodium bicarbonate should be added to each pint of saline. The solution should be slowly injected through a long soft tube, and the patient should be instructed to retain it as long as possible.

*Intraperitoneal injections*—Saline solutions may also be injected into the peritoneal cavity, whence they are absorbed more rapidly than from the subcutaneous tissues. This method is specially useful in children, in whom it may be difficult to find a vein large enough for intravenous transfusion. The injection may be performed by means of a stout intravenous needle, but Rogers devised a little instrument for the purpose, consisting of a steel cannula, the distal end of which is sharpened like a cork borer, a flange near the other end prevents it from slipping in too far. The instrument is provided with a blunt stylette. An incision, half an inch in length is made with a narrow bladed knife, just below the navel in the mid line of the abdomen. This position is chosen because the peritoneum, being adherent to the umbilicus, will not strip in front of the cannula, unless first perforated. The injection is made by means of a bulb, holding a sterile salt solution attached by a rubber tubing to the cannula. For an adult man two or three pints may be rapidly run in, from a height of two to three feet within ten minutes. Not more than three pints should be given at a time although, after the saline has been absorbed, the process may be repeated through the same incision. Should any embarrassment to the patient or any difficulty in breathing be produced by the injection, the operation must instantly be stopped.

*Treatment of collapse and suppression of urine*—In the stage of collapse, when suppression of urine has occurred. A. W. Sellards has successfully established the urinary flow by giving in addition intravenous injections of 2 per cent sodium bicarbonate. The objection to using this salt is that it exerts a lytic action on the red cells *in vitro* and may cause convulsions, but in 4 or 5 per cent concentration it has no hæmolyzing effect. It is thought that possibly, by sterilizing and heating, the bicarbonate is converted into carbonate and this is injurious, but Sellards found that by sterilization in an autoclave connected with live steam at 7 lb pressure, this conversion was minimized so that only 25 per cent of the bicarbonate was converted into carbonate in one hour.

Other methods have been used to re-establish the urinary flow. Hamilton Bailey and others have recently recommended the intravenous drip isotonic sodium sulphate method, and this is worthy of consideration. Pituitary extract may be given,  $\frac{1}{2}$ –1 c.c. being injected hypodermically two to four times a day. Adrenalin, also, may be used for the same purpose. Caffeine citrate 5 grains, is useful as a cardiac tonic, and may be given three or four times during the twenty four hours, a mixture containing 5 minims of tincture of

atrophanthus administered three times a day, may be employed as an adjuvant

Local stimulation may be applied to the kidneys by means of hot fomentations to the lumbar region, supplemented by rectal injections of hyperalkaline saline, i.e., 150 grains of sodium bicarbonate to the pint of normal saline. This should be administered slowly every two to four hours in cases in which the collapse appears to have been overcome but suppression of the urine persists

**Treatment of the reaction stage**—If purging should still persist large doses of salicylate of bismuth, with a little opium, are useful. Injections of digitalin 1/100 grain are given to stimulate the cardiac action. Retention of urine may actually occur, the bladder should be examined for this reason and if necessary, a catheter should be employed. Should the patient then become constipated, purgatives must be avoided, simple enemas being employed instead.

**Treatment of convalescence**—In the absence of complications and with careful regulation of the diet cholera patients recover their strength with remarkable rapidity except the very old or those who have previously been in ill health. It is specially necessary to permit no sudden exertion such as sitting up in bed for a few days as the heart is necessarily exhausted after such a strain. Once however a fairly full diet can be given safely convalescence is very quick, and it is possible to discharge a patient within ten days of the cessation of acute symptoms. About the only satisfactory feature of this disease is the rapidity with which restoration to health takes place.

**Nursing precautions**—It must never be forgotten by those in charge of cholera cases that the discharges are a danger to everyone concerned and that they may contain the vibrio for as long as forty days after the attack. The germ dies quickly when dry, but it reserves its vitality for many days in damp and soiled linen. It cannot be killed by ordinary cold. Therefore the most strict precautions should be taken to disinfect all soiled linen from cholera cases in a 2½ per cent cresol solution. Every care must be taken also to prevent contamination of the water supplies or of any drinking vessel.

**Mortality**—The average case mortality in cholera amounts to about 50 per cent. Some epidemics are more deadly than others and usually the death rate is greater in the earlier than in the later stage of an epidemic. In such an exhausting disease it is the very young or the very old who show diminished powers of resistance. From statistics given by Rogers (1923) it is seen that fewest deaths occur in the second decade from eleven to twenty years of age, and that the mortality rate rises steadily with each subsequent decade, to reach a high figure in those over fifty years of age. In those who are subjects of grave organic disease and in the dissipated, starved and feeble, the danger from cholera becomes increasingly great. In the Indian statistics especially those from the Calcutta Medical Hospital, the

highest mortality rate is amongst the Hindus, who are largely vegetarian in their diet. It is slightly lower among the flesh eating Moham medans, and still lower among the Eurasians and Europeans. Cholera is particularly virulent in pregnant women.

Rogers has given details of the mortality rate in India since the early days of last century. During the great Bengal epidemic of 1817-23, it was put down by different observers as from 60 to 70 per cent. In 1860, Morehead gave the following approximate estimates.

For native troops coming early under treatment it was 30-45 per cent, in European General Hospitals, 50-55 per cent, and for large native civil populations, 60-65 per cent. It must be borne in mind that during epidemics of cholera it is a well accepted fact that the mortality is exceedingly high at the beginning and progressively decreases throughout its course. Macpherson recorded an outbreak at Karachi in which the mortality among the first hundred cases was 79, in the second hundred 66, in the third 50, and in the fourth only 40, little more than half that in those who were first attacked. Rogers points out that if these facts are not carefully borne in mind remedies used in the earlier cases may be regarded as quite useless while those administered towards the end of the outbreak may be undeservedly lauded.

**Prophylaxis**—At the present time little attention is paid to quarantine regulations as a means of preventing the entrance of cholera, because convalescent patients may pass the vibrios in their stools for as long as forty four days from the commencement. In the Naples epidemic of 1911 90 per cent of the cases were traced to direct contact with patients or healthy carriers, and in the Colombo outbreak of 1926, out of 442 contacts examined, 10 per cent were found to be carriers of the cholera vibrio.

In Great Britain practical measures are relied upon for the exclusion of cholera. Under this system only ships which are or have been carrying cholera patients are detained and then merely until they can be thoroughly disinfected. By this method merchants and travellers suffer but small inconvenience and loss and the temptation to conceal cases has been thereby avoided. Any suspicious cases occurring on shore are at once reported to the sanitary authorities and promptly dealt with, and every endeavour is made to prevent the faecal contamination of the public water supplies.

In India, during recent years the prevention of cholera has been on much the same lines attention being directed to sanitation rather than to quarantine regulations. This is specially the case in dealing with the multitudes which collect at the great religious festivals, great care being taken to provide pilgrims with good drinking and bathing water.

Some authorities consider that the mixture of essential oils, if given in one drachm doses in half an ounce of water, is a good preventive, and

it is possible that by this means contacts in association with a case can be protected

*Sterilization of water*—The cholera vibrio has been described as being capable of living in fresh water from two to sixty eight days and in distilled water as long as twenty days. In salt water it may live for a considerable time. One to three per cent of salt does not inhibit its growth although 5 per cent is more effective.

*Disinfection of wells*—In most parts of India the water supply of villages and towns is derived from wells which are very liable to contamination during cholera outbreaks. It is here that potassium permanganate in the strength of 60 grains to the gallon of water appears to be invaluable. This strength renders the water pink. It should be left to stand until it has been colourless for twenty four hours and at the same time all vegetation and aquatic insects if present should be removed. Potassium permanganate appears to act by precipitating all the organic matter in suspension rather than by actually killing off the organisms. It is also possible that it acts by destroying the toxins given off by the vibrios. A bucket containing the permanganate salt is lowered gently into the water till it is filled it is then drawn up, and the water is poured carefully into the well the undissolved crystals not being allowed to escape. This process is repeated until the whole is passed into solution.

*Cholera phage*—Recently J. Morrison has advocated the employment of cholera bacteriophage (cholera phage) as a means of preventing water borne infection with the cholera vibrio. This method has been tested in selected districts in Assam which it is claimed have now been free from cholera for twice as long a period as any during the last ten years.

S. L. Mitra (1933) states that cholera phage was introduced into Bihar Province India in 1931. The results both as curative and prophylactic agent appeared highly encouraging, and since then its use has been extended over the Province in an increasing degree.

*Inoculation*—The present method of inoculation against cholera owes its origin to the pioneer work of J. Ferran in 1885. He first demonstrated that guinea pigs could be protected against lethal doses of cholera by subcutaneous injections of living vibrios. After this over fifty thousand people were inoculated against cholera in two years during the great outbreak in Spain. This method was then condemned because of the numerous accidents and grave reactions that were said to have taken place. It is doubtful how many lives were saved by this vaccine.

In 1892 Haffkine modified Ferran's method of prophylactic inoculation. For this purpose he first obtained a very virulent strain of organisms by twenty to thirty passages intraperitoneally through guinea pigs. For the first dose an attenuated virus was obtained by cultivating the organism in broth at 39° C in a constantly aerated atmosphere. A few days after inoculation of this weakened virus the



exalted ones could be given safely, and this was found to produce an immunity to all subsequent methods of infection

It has since been discovered that a negative phase of decreased resistance to this disease occurs for two to four days after the first dose, but there is little evidence that this enters in an important degree into prophylactic measures. It is important to note that the vaccine must not be kept longer than three months, also that the protection afforded is comparatively short—usually about six months

Haffkine spent many years inoculating over seventy thousand persons with his vaccine. The results he obtained were, on the whole, distinctly favourable, and the value of his method is borne out by subsequent statistics, e.g., those obtained in the Balkan War of 1913, in Batavia in 1915 and 1916, and throughout the course of the 1914-18 War in different parts of the world

The reactions produced by the cholera vaccine are usually mild, and the only people for whom inoculation is contra-indicated are infants under two years, and persons suffering from any gastro-intestinal trouble. As at present constituted, the vaccine consists of an emulsion of the organisms amounting to eight thousand million per cubic centimetre. The initial dose is  $\frac{1}{2}$  c.c., this being followed ten days later by 1 c.c.

*Immunization by the mouth*—In Russia and in France great store has been laid upon the method of vaccination by the mouth originally advocated by Bestredka. This method is specially useful where the immunization of large numbers of people is necessary. The vaccine is made from dense suspensions of the organisms killed by heat, carbolic acid, or alcohol, and is given in from three to five doses ranging up to 100 c.c. every other day. Each dose consists of 10 to 100 milliards of vibrios, or 0.01 to 0.1 gramme of the dried organisms. The mixture of the dried vaccine with bile is known as 'bili vaccine,' and has been used by the French in Indo-China. Usually these pills are harmless; sometimes they may cause diarrhoea. A. J. H. Russell (1927) has made a comparative test of the results obtained by the use of anticholera vaccine and of oral bili vaccine. He considers that in the presence of a cholera epidemic there would be an objection to the administration of oral vaccine. In 1448 villagers who were given two doses of anticholera vaccine, there occurred six cases and one death, but in 3085 persons who received three doses of bili vaccine, fifteen were attacked and three died. In an epidemic at Tokyo when oral vaccination was carried out at the height of the epidemic, there were only three cases among 300,000 people vaccinated, whilst in the three million unvaccinated more than six hundred cases were noted.

*Personal prophylaxis*—During cholera epidemics great care must be exercised in preserving general health. Dietetic and alcoholic excesses must be specially avoided, and visits to the cholera districts should be postponed, as newcomers are especially likely to contract the disease. The eating of unripe or over-ripe fruit, shell fish, or any thing else which is likely to upset the digestion, is dangerous. All drinking water and all water used in the washing of dishes must be boiled; mere chlorination with bleaching powder (1.8 per cent. of

chlorine per million, or 2 grammes of the powder to every 110 gallons) is not to be depended upon. Sodium bisulphate tablets (2 grammes to  $1\frac{1}{2}$  pints of water), by liberating sulphuric acid, provide a useful method of sterilizing water, for instance, in a water bottle. It is not advisable to trust to filters alone except the Pasteur Chamberland type, as they may be more likely to contaminate the water than to purify it. In households or institutions, abundant quantities of weak tea or lemonade should be provided during a cholera epidemic, the supplies being renewed daily. This ensures the boiling of water in the preparation of drinks. Food must be protected from flies.

## The Steatorrhœas

## CHAPTER XX

### PELLAGRA (AVITAMINOSIS B<sub>2</sub>)

**PELLAGRA**, a syndrome implicating digestive, nervous and cutaneous systems, must be regarded as a typical avitaminosis. Although the digestive phenomena may not always dominate the clinical picture yet they may play a prominent part, so that it now has claims to be included amongst the "Dysenteric Disorders".

**Definition.**—Pellagra is a typical syndrome—diarrhoea dermatitis and dementia—which is the outward expression of an inward avitaminosis, due to the absence of vitamin B<sub>2</sub> in the diet or of its destruction in the alimentary canal interfering with absorption and assimilation.

**Geographical distribution**—Long thought to be confined to Italy, the Iberian Peninsula and the Balkan States, pellagra is now known to have a world wide distribution. It has been reported from Portugal, Spain, S. W. France, Denmark, British Isles, Germany, Hungary, Austria, Yugoslavia, Bulgaria, Roumania, Greece, Bessarabia, Russia in Europe, and Poland.

*In Africa* pellagra is prevalent throughout the whole continent but especially in Egypt, Nyasaland and amongst the Kaffir and Zulu races.

*In Asia* it occurs in Asia Minor, especially in Syria and Armenia. In India, the Philippines, Japan, China, Korea and Manchuria.

*In America* it is found in Canada and the United States, especially in S. States, Mexico, Brazil, Argentine and West Indies.

*In Australasia* it has been reported from New Caledonia and Melbourne.\*

**Epidemiology.**—It is probably true that, once recognized in a district, pellagra is generally found to be much more common than was previously considered possible. It has long been noted that the number of patients fluctuates markedly from year to year. This may be ascribed mainly to dietetic factors but also to the incidence of debilitating diseases which, as is now known, may prove determinative, such as ancylostomiasis, malaria, bilharziasis, tuberculosis, the stercororrhœas including sprue, amœbic and bacillary dysenteries and even syphilis. Chronic alcoholism, intestinal tuberculosis, chronic dysentery or operation on the gastro intestinal tract (gastrojejunostomy or colectomy) may so interfere with normal absorption as to produce secondary pellagra (see p. 834).

In countries with marked seasonal variations pellagra appears in an

\* For further information see Stannus H.S. (1936) *Trop. Dis. Bull.* 33: 7-9.

acute and epidemic form in the spring and autumn the former being usually the more severe. In the southern hemisphere the reverse is the case. In the Northern United States, spring and autumn cyclical appearances are the rule but in the South it may appear at any season. It is probable however, that climatic factors play but an indirect part in the aetiology.

**Sex**—Both sexes are liable, it may be that in different cases it may exhibit a distinct preference for one or other according to local occupation. In the United States however, it is distinctly more prevalent in women where domestic work, pregnancy and lactation are considered determining factors.

**Age**—All ages may be affected, but the majority of cases occur between 20 and 50. Infantile pellagra is now well recognized and has been considered a distinct variety. It has been reported especially from Italy, America, India, China and E. Africa.

**Economic status**—Naturally occurring pellagra is essentially a disease of the poor and indigent. It is primarily a disease of agricultural labourers even in the heart of pellagrous districts the urban inhabitants escape. It has been pointed out that it is extremely infrequent in the Jewish race.

**Aetiology**—Since the days of Lombroso and Bellardini (1871) the occurrence of pellagra has been connected for apparently cogent reasons with the consumption of maize usually diseased. It is a fact that pellagra diminished concurrently with improvement in the method of storing and preparing this cereal for human consumption. Hard physical labour is undoubtedly also a predisposing factor emphasized by Wilson (1921). The implicit belief in maize as the sole aetiological agent was rudely disturbed by the discovery of isolated cases in England and in N. Europe generally where this cereal does not form the staple article of diet.

W. F. Deeks and C. Funk in 1913 first definitely suggested that pellagra is a diet deficiency disease due to lack of certain vitamins and the latter succeeded in isolating them from yeast and rice. The experiments of J. Goldberger and G. A. Wheeler in U.S.A. on the experimental reproduction of this disease in humans supported this hypothesis. The pellagra which was extremely prevalent in Turkish prisoners in Egypt in 1919 was traced by the investigating commission to errors in metabolism due to a primary deficiency of biological protein.

The next step was made by G. A. Wheeler and J. Goldberger in 1922 who found that yeast was effective in the prevention and treatment of black tongue disease of dogs and also in human pellagra. Since then black tongue (or canine typhus) has been regarded as the analogue of the naturally occurring disease in man. This gave rise to the hypothesis of a PP (pellagra preventive) factor contained in yeast, liver and other foodstuffs. Shortly afterwards J. Goldberger and his colleagues

were able to identify the PP factor with a vitamin which differed from the antineuritic vitamin (aneurin or thiamin) in its distribution and heat stability. This has now been identified to a great extent with the vitamin B<sub>2</sub> complex (or nicotinic acid, nicotamide), mainly as the result of the work of Spies and his colleagues on the successful treatment of pellagra in man with this substance (see p. 335).

Nicotinic acid (the PP factor, sometimes known as vitamin B<sub>2</sub> or in U.S.A. as vitamin G) is the carboxylic acid of pyridine, prepared by the oxidation of nicotine. The amide is known as nicotamide. Both these substances have been found to be essential in meat infusions necessary to the growth of bacteria, especially *Staphylococcus pyogenes* and the diphtheria bacillus. Both are capable of preventing and actually of curing black tongue disease of dogs and other manifestations of pellagra in laboratory animals (C. A. Elvehjem *et al.* 1937). The exact function of nicotinic acid in the human body is not yet clearly understood. It is known that nicotamide is part of the molecule of the co-enzyme which plays a part in carbohydrate metabolism.

The richest sources of nicotinic acid under natural conditions are yeast, liver, kidneys, milk, eggs, and cheese. A colour test is described for its detection in urine which has been found negative in pellagrins though positive in normals.

The original vitamin B<sub>2</sub>, now known as riboflavin (or lactoflavin) is a yellow fluorescent pigment which is found in liver, eggs and milk and is responsible for the greenish yellow fluorescence of whey. When isolated in a pure state it is a golden brown solid (6-7 dimethyl-9 ribityl [d-1-ribityl] isolloxazine).

Probably riboflavin is an enzyme concerned with oxidation processes in the body cells and, in bringing about metabolic changes, it acts in combination with phosphoric acid—in a process known as *phosphorylation*—which is essential for the absorption of fats by the intestinal epithelium of the villi of the small intestine (see p. 353). It is now thought to be associated with angular stomatitis (cheilosis) of pellagra and associated diseases, with the seborrhœic excrescences on the nose and the nasolabial folds in this disease (ariboflavinosis) with acne rosacea and rosacea interstitial keratitis. Riboflavin cannot be synthesized by the human organism. The rat anti-dermatitis factor (B<sub>6</sub>) is now thought to be distinct from the PP factor. A pellagra-like disease in rats is caused by deprivation of this substance which is found especially in mammalian liver and in muscles of the salmon, herring and haddock. Another is now known as the chicken pellagra factor.

**Pathology.**—*The essential pathological lesions of pellagra are difficult to observe on account of the frequency of complicating diseases, such as malaria, ancylostomiasis, chronic bacillary and amœbic dysenteries and occasionally intestinal tuberculosis. According to modern conception, all these should be regarded as predisposing factors. Great emaciation is constantly observed. The viscera show chronic degenerative changes, such as fatty infiltration, and characteristic deep pigmentation.*

tion The intestinal walls, especially the large intestine, are attenuated and diaphanous (*see also* sprue, p 348), the mucous membrane being inflamed and often ulcerated The liver, spleen and heart are atrophied, the latter often wasting 2-3 ozs and showing 'brown atrophy' Atrophic changes in the suprarenals were also observed by the author during the last war (1916)

The changes in the central nervous system are significant There may be actual wasting of the brain substance, and the ventricles are distended The lateral columns and crossed pyramidal tracts of the spinal cord are implicated Perivascular pigmentation of the cerebrum and cerebellum and midbrain was noted by the author in autopsies in Egypt (1916) The anterior cornual cells are atrophied and pigmented The posterior columns, however, do not entirely escape The degenerative changes in the lateral columns are seen in the middle and lower thirds of the dorsal region With all these changes the cerebrospinal fluid is normal, with no increase of the globulins As an explanation of this Mott originally stated that there are no alterations in the meninges, though the changes in the nerve cells resemble those of a chronic toxæmia The posterior spinal ganglia cells exhibit chromatolysis disappearance of Nissl's granules and chromatolysis of the cells of Clarke's column Similar changes, but of lesser degree are seen in the Betz and Purkinje cells of the cortex In short the nerve lesions in pellagra point to a close relationship between beri beri Korsakoff's syndrome, subacute combined degeneration of the cord and central neuritis" (the last, described by H H Scott in Jamaica and more recently in Sierra Leone and Nigeria is probably a pellagrous condition)

**Diagnosis and differential diagnosis**—Difficulty in diagnosis arises mostly in sporadic cases, and in secondary pellagra appearing in non endemic areas, but when localized erythematæ resembling exaggerated sunburn turn up in numbers, associated with digestive and nervous (mainly mental) manifestations, and especially when there is a seasonal recurrence, pellagra can hardly be confused with any other disease

Frequently the rash has at first been confused with some fungus infection of the skin, with lupus erythematosus, with acrodynia syphilis or some toxic dermatitis or the glossitis, stomatitis and gastro intestinal disturbances may closely resemble sprue (to which, as the sequel goes to show, they are closely related)

The nervous manifestations may have to be differentiated from hysteria melancholia, general paralysis of the insane and cerebral syphilis As there are so many border line cases, and in view of the fact that pellagrous manifestations may be engrafted upon those of sprue, idiopathic steatorrhœa, cœliac disease, beri beri and occasionally associated with scurvy and chronic alcoholism absolute diagnosis may be attended with considerable difficulty It is becoming more and more recognized that multiple vitamin deficiencies in man are the rule rather than the exception Davidson has pointed out with some

emphasis that, even if one clinical syndrome dominates the picture multiple deficiencies are generally present. This applies to deficiency states conditioned directly by ingestion of insufficient diet, or indirectly by failure in digestion and absorption.

The Plummer Vinson syndrome, which has been described in middle aged women, has many symptoms in common with pellagra. Pink disease in children, which is probably an avitaminosis, may also be mistaken for it, as may also lathyrism and ergotism.

Under the name of "crazy pavement skin eruption" L. Nicholls (1940) refers to a condition common in Ceylon and indeed in all emaciated natives, especially in Indian seamen (personal observation). Described originally by C. D. Williams (1933) it is common in otherwise healthy children in Tanganyika (A. MacKenzie, 1941). There is a tendency to associate this lesion with pellagra.

The diagnosis of pellagra rests mainly on the character of the clinical manifestations reinforced by laboratory investigations such as those for achlorhydria, blood examination and more especially porphyrins in the urine. In exceptional cases the diagnosis may have to be made by a process of exclusion.

### SYMPTOMATOLOGY

Pellagra is a disease, as A. D. Bigland (1920) so aptly remarked 'difficult to diagnose and often overlooked unless the possibility of its occurrence is kept in mind'. It has often been emphasized that in the endemic areas (L. J. Harris, 1939) the majority of cases never develop all the classical symptoms of the disease so that more and more attention is being directed to pellagral states, 'pre pellagra', 'larval pellagra' or the *formes frustes* of Stannus.

Pellagra is usually drawn out, it does not run a stereotyped course but is liable to exacerbations and remissions.

**Prodromal**—The initial symptom may be a combination of psychical and digestive disturbances and recur for years in the absence of the typical dermatitis. *Larval pellagra* (or pre pellagra) manifests itself by anorexia with dyspepsia, mental depression, often neurasthenia, constipation and occasional attacks of diarrhoea. A sore mouth with glossitis and angular stomatitis, the tongue being swollen with marginal indentations, is common (see p. 362), an atrophic condition of the lips (perlèche) often may be an accompaniment. These tongues were first described by H. S. Stannus in Nyasaland and about the same time by the author in Ceylon. Often there are eye symptoms and lachrymation and maybe roughening of the skin on elbows and knees (*phrynoderma*). The disease process may be arrested at this stage or proceed to full development.

**Gastro-intestinal symptoms**—From the specialized standpoint of this work the digestive manifestations of pellagra, which have hitherto hardly received the attention they deserve are of special interest. In the early stages the lower part of the abdomen and epigastric region



are rigid and painful. Usually there is gaseous diarrhoea and occasionally pale fatty, fermenting stools resembling those of sprue (see p. 350). The association of manifest pellagra with this sprue like diarrhoea has led to the consideration of a link between these apparently distinct diseases. This was noted by C. G. Manning (1909) who referred to pellagra in the West Indies as 'Pilois pigmentosa'.

Recent investigations have stressed the frequency of achlorhydria in at least 40 per cent. of these early cases and hypochlorhydria in the remainder which as Stannus has pointed out may possibly represent the initial feature of the pellagra producing process and denote a preliminary gastritis. This fundamental resemblance between pernicious anaemia and pellagra has impressed itself on the minds of many observers. (On the other hand it should be noted that chronic gastritis with resulting failure of gastric acid secretion and achylia gastrica is not uncommon in native races (de Langen) and yet pellagra is apparently as rare amongst them as is pernicious anaemia.)

**Anæmia**—The anæmia associated with pellagra is irregular in incidence and no direct relationship can be established between its degree and the severity of the disease nor between the occurrence of anæmia, achylia or diarrhoea (cf. also sprue). Not only is the degree but also the type of anæmia irregular—it may be slight hypo- or hyperchromic and of varying colour indices. In this respect it has been pointed out that there are resemblances to sprue and also to the hypochromic anæmia of Wits, but it has also been shown by T. D. Spies and W. Payne (1933) and later by M. Salah (1935) that in pellagra in spite of the variations of the acidity curve the 'intrinsic factor' is being secreted by the stomach.

**Skin manifestations**—*Pellagra dermatitis*. Formerly most observers regarded the skin lesions as the earliest manifestations of the disease but most probably they are symptomatic of the more advanced fundamental disturbance. At first an erythema which resembles a severe sunburn is observed on those parts of the body exposed to the sun. The eruption is symmetrical and undoubtedly photosensitive—usually the patches are irregular in outline and vary in intensity. They appear on the back of the hand and dorsum of the foot then on forearms, legs, chest, face and neck and sometimes on the scrotum and female genitalia. The affected areas are swollen and tender and the seat of burning and itching sensations. Sometimes petechiae are seen and more rarely, bullae or blebs with clear or blood stained contents. The eruption usually lasts a fortnight and is followed by desquamation which leaves the skin rough and thickened and usually permanently stained a sepia colour. This is especially noticeable on the back of the hand and is usually evident at the base of the neck like a rosary—hence it is generally known as Casal's necklace. The acute stage usually lasts fourteen days, after two to three months the main symptoms abate and although the affected skin areas remain dark and rough the disease

process appears to be arrested but the following spring the dermatitis reappears in an exacerbated form and for several years it may recur with increasing severity.

There is wasting of the smaller muscles of the hands and wrinkling of the skin which give the appearance of washerwomen's fingers.

One of the most constant subjective symptoms is burning pain and tingling in the hands and soles of the feet these are probably the same as those felt elsewhere in the skin and comparable with the lesions in the mouth and tongue.

Obstruction to the sebaceous ducts on the nose and *alæ nasi* produce a peculiar sulphur flaked appearance of the skin which varies in different races and it is to this that Stannus has applied the term *folliculitis*.

Œdema is usually present it may be universal as in nutritional œdema and was common in the series observed by the author and A. D. Bigland in Egypt (1920). It is found especially in the lower extremities and is then reminiscent of a similar œdema in cardiac beriberi.

**Nervous symptoms**—Implication of the nervous system manifests itself by tremor of the tongue and face muscles by exaggerated reflexes and often by mild dorsal spinal tenderness. Muscular cramps are common. The patient is the victim of either insomnia or uncontrollable somnolence. He is conscious also of great weakness especially of the lower extremities. Chvostek's sign is usually present. Depression develops into melancholia maybe with maniacal interludes with a tendency to suicide. Finally the pellagrin becomes emaciated paralysed completely demented and bed ridden and generally dies from diarrhoea urinary incontinence exhaustion or intercurrent disease.

**Urine**—In recent years much interest has been centred in the urine which is usually alkaline it may also contain tube casts albumin and usually indican. There is generally coproporphyrinuria and as emphasized by W. Beckh and P. Ellinger (1937) this is especially noticeable in the alcoholic variety. Furthermore T. D. Spies, Y. Sasaki and E. Crooks (1938) have shown that the amount of porphyrin in the urine is directly proportional to the nicotinic acid intake. The derivation of this porphyrin is a matter of debate. As pointed out by L. Rau (1940) there are cases of congenital porphyrinuria with photosensitive skin lesions not connected with pellagra. Porphyrinuria may be referred to hypersensitivity to nitro and amino bodies produced by the intestinal dysfunction or possibly associated with increased destruction of blood pigments.

**Infantile pellagra**—Recently much has been written about pellagra in children and some of these indefinite clinical states have been designated *pellagroid*. There appears to be no reason for this artificial subdivision. The clinical appearances may however be so divergent that their nature may be overlooked especially in native races.

These children are vexatious and irritable the skin and hair tend to lose their normal colour and sheen. There are usually gastro intestinal symptoms with diarrhoea and transient oedema of the hands and face. After ten days pigmented patches of dermatitis appear around the ankles knees wrists and elbows especially (it has been emphasized) at the points of irritation or of pressure. Lowell described infantile pellagra as a syndrome whose principal signs are oedema dermatitis and diarrhoea in infants it has been known as Williams Disease (Kwashiorkor W Africa) nutritional oedema with pellagra *Culebrilla* (ringworm disease) in Mexico pellagroid beriberi (Cuba) *Cachexia hydrique infantile tropicale* (Salvador) oedema of avitaminosis (Costa Rica). It occurs as an endemic disease. Sporadic cases have been noted in U S A China and under war conditions in Europe. Acute pellagra is commonly associated with nutritional oedema and decreased serum albumin as in cases described by Bigland (1920). The skin condition closely resembles skin lesions seen in pellagrin negro infants in America. There is no evidence to suggest beriberi as a common cause of the oedema while it does not improve after injections of crystalline B<sub>1</sub> (aneurin). Three out of seven cases make a good recovery on nicotinic acid.

**"Pellagra typhus"**—In this acute and fulminating form there is high pyrexia prostration muttering delirium pronounced nervous tremors generalized rigidity and not infrequently epileptic form convulsions. Death may take place in as short a period as three weeks.

**Pellagra due to voluntarily restricted diet**—A number of authentic instances have been recorded and collected by Stannus. They are most interesting as proving that the disease can be produced by withholding the extrinsic factor or factors from the diet. All cases have arisen in faddists following some cult who for some health reasons have adopted an unbalanced diet or it may be a letogenic diet under medical direction. There is a striking similarity between cause and effect in all those cases described by W H Mook and R S Weiss (1925), P S Carley (1928) S A Munford (1930) R H Guthrie (1930) N P Walker and G A Wheeler (1931) and J F Holst (1935).

**Secondary pellagra** is now generally acknowledged to be a definite clinical entity. In all its manifestations pellagra is connected with some organic lesion of the gastro intestinal tract. The following is a list—oesophageal stricture carcinoma of stomach carcinoma of the alimentary tract especially of the transverse and descending colons ulceration of colon pyloric ulcer and stenosis after operation for gastric ulcer duodenal feeding carcinoma of head of pancreas and of ileum stricture of jejunum tuberculous enterocolitis stricture of rectum (lymphogranuloma inguinale) polyposis rectovaginal fistula multi lobular cirrhosis of the liver and diaphragmatic hernia.

**Alcoholic pellagra.**—In the northern portion of the United States alcoholic pellagra has been recognized as not uncommon. The term "alcoholic pseudo-pellagra" has now been abandoned. The pellagra syndrome may be secondary, through disturbance of normal digestion by alcohol, or it may be due to difficulties in feeding. Isolated alcoholic cases have been recognized also in Berlin, Austria and in France. E. R. Maloney has published a series of twenty one cases. Symptoms appeared within two to six weeks after drinking crude whisky with little more than a plate of soup a day. Two had delirium tremens. The pellagrous rash appears on the hands and face, but never on the feet.

**Pellagra in the insane.**—Naturally occurring pellagra may lead to insanity or, conversely, those insane from other causes appear to be specially liable to pellagra. This distinction has not been recognized as much as it should be, and S. R. Roberts (1929) estimates that 10 per cent. of the insane are apt to develop pellagra. This is now accepted in the United States where Goldberger found that in certain asylums the number of lunatics developing pellagra each year was a constant proportion of the total. In England pellagra is not uncommon in lunatic asylums. G. A. Watson (1928) in a report from the Lancashire County Mental Hospitals, stated that, though in some cases the disease was present on admission, in the majority it appeared after six months' to several years' residence.

#### TREATMENT OF PELLAGRA

It is generally conceded that great advances have been made in recent years in the treatment of pellagra. These have been so important as to have far-reaching repercussions in many directions. Goldberger and Wheeler first noted that great improvement took place in what was formerly regarded as the most intractable stages of this disease—the dermatitis and nervous lesions—when the patients were fed on a diet rich in proteins and vitamins. Liver and yeast were regarded as particularly specific, especially the extract of yeast known as "marmite."

Then in 1937 C. A. Elehjem, R. J. Madden, F. M. Strong and D. V. Wooley reported the cure of black tongue in dogs with nicotamide obtained from yeast. Later T. D. Spies, C. Cooper and M. A. Blankenhorn (1938) recorded successful treatment of human cases with nicotinic acid in large doses (40–80 mgm. by injection, or 200–1,500 mgm. by mouth) within twenty four hours. Shortly afterwards there followed similar favourable reports by P. J. Fouts, O. M. Helmer, S. Lipowsky and T. H. Jukes (1937) on alcoholic pellagra. T. D. Spies, W. B. Bean, and R. E. Stone (1938) found, in a series of 78 cases of endemic and 99 subclinical pellagra, not a single case which did not respond almost immediately to nicotinic acid therapy. T. D. Spies, C. D. Aring, J. Gelperin and W. B. Bean (1938) had similar results in 60 cases with acute mental disturbances and intestinal manifestations, even within as short a period as ten hours with daily doses of 500–1,000 mgm. of

nicotinic acid by the mouth, occasionally 100 mgm were given intravenously

These favourable American results have been confirmed in Egyptian pellagra by A C Alport P Ghalioungui and G Hanna by P Lilinger A Hassan and M M Taha (1937) and others They find that on the whole, the glossitis and aphthous stomatitis are most promptly affected and ulceration disappears in four days with return of the taste sense The skin lesions were similarly affected More recently it has been reported that pyralism Vincent's spirochaetal infection of the oral cavity and coproporphyrinuria were similarly improved

The present evidence is therefore that nicotinic acid cures pellagra and also the parallel avitaminosis of dogs and pigs and it may be that the virtue formerly ascribed to liver extracts in these conditions may be due to their nicotinic acid content

In normal individuals (not suffering from avitaminosis) nicotinic acid produces a histamine effect—increased warmth and tingling—in the face and neck but occasionally nausea vomiting and abdominal cramps It is essential that nicotinic acid treatment should be reinforced by a liberal protein diet and maintained for several months The normal dose of nicotinic acid is 150 mgm a day but in severe cases 900 mgm or even 1 000 mgm may be necessary

In cases with severe intestinal disturbance where the nicotinic acid may not be absorbed the injection of a suitable soluble preparation is indicated *Coramine* (diethylamide of nicotinic acid) which has long been used as a cardiac stimulant (2.5 cc solution up to 20–50 cc) appears to be equally efficacious C E Bills F G McDonald and T D Spies (1939) find that Pyrazine 2–3 dicarboxylic and Pyrazine monocarboxylic acids also possess formidable antipellagrous properties Moreover R W Vilter and T D Spies (1939) have also shown that quinolinic acid (2–3 dicarboxylic acid of pyridine) which is the homologue of the above also cures the acute glossitis

## CHAPTER XXI

### SPRUE AND HILL DIARRHŒA

**Synonyms.**—*Psilosis*, *Aphthæ tropica* (German), *Athrepsie coloniale atrophique* (French)

The term "sprue" has long been used in the Netherland Indies as indicating some form of chronic diarrhœa. It was first introduced to English medical literature by Manson when he anglicized the Dutch 'Spruw' (as used by Van der Burg) into sprue. It should be mentioned that an aphthous stomatitis, which is frequently seen in badly nourished children and women and which was popularly known in Holland as *spruw* has no apparent relation to tropical sprue.

Many are the names which from time to time have been bestowed on tropical sprue—*Aphthoides chronica*, *impetigo primarum viarum* (Hillary 1766), *Indische spruw*—*aphthæ tropicæ* (Van der Burg), *psilosis linguae vel mucosæ intestini* (Thun 1897), *cachexia aphthosa*, *stomatitis intertropica*, and *aphthæ orientalis*. It was known to the older generation of Indian physicians as white flux, white purging, white chronic diarrhœa, scorbutic diarrhœa, or chronic enteritis of Indo-China. In Ceylon it is still popularly termed "sore mouth," in Malaya "Singapore sore mouth."

**Definition.**—The name sprue is given to a tropical and subtropical disease which manifests itself by catarrhal inflammation of the whole or part of the intestinal tract. It is distinguished by a chronic diarrhœa with passage of large, pale, mucous stools, together with a peculiar inflammation of the tongue, mouth, and œsophagus, progressive emaciation, and, finally, marked anæmia of the pernicious type.

Although pre-eminently a disease of warm climates, symptoms may arise for the first time in England or any part of the Northern hemisphere in persons who have previously resided in the tropics.

**History.**—Although sprue was recognized as a distinct disease and given a great variety of names by the earlier physicians who practised in India and the Dutch East Indies, the first accurate description is undoubtedly that given by Vincent Ketelaar in 1669, in a work which was reprinted several times. In *Observations on the Changes of Air and concomitant epidemical diseases in the Island of Barbados*, an account of what appears to be sprue is given in detail by Hillary in 1766. The name "sprue" was first applied in descriptions written independently by Van der Burg in Java and Manson in Amoy, China, in 1880.

After the occupation of Annam, the French referred to sprue as "entéro colite endémique de Cochinchine" and the writings of Berenger Feraud, Kelsch and Kiener convey the impression that sprue should be regarded as a sequel to some form of dysentery.

In 1897 G. Thin published "Psilosis or Sprue," containing a summary of the then existing knowledge, in which he illustrated various lesions of the sprue tongue and gave an accurate description of treatment by milk or fruit diet. In 1906 there appeared a valuable summary of knowledge by A. G. Rademaker, and in 1908 a monograph appeared from the pen of W. Carnegie Brown.

**Ætiology** *Predisposing causes* —Although there are strong reasons for regarding sprue as a disease *sui generis* yet there is a considerable amount of evidence that other well known and specific infections of the alimentary tract may predispose to its development. Of these amœbic and bacillary dysentery take the first place, though the evidence that these are necessarily precursors of sprue is not convincing. In a series of two hundred cases in which this point was investigated by the author a previous history of intestinal infection was found in 40.5 per cent, and amœbic dysentery in 32 per cent.\*

Sometimes sprue and amœbic dysentery co-exist in the same patient, as in the following instances —

A very severe case was seen in a man forty five years of age who had lost 76 lb and weighed only 120 lb. The general appearance of the patient, with sore tongue, emaciation and large frothy stools, was typical of sprue and in addition blood and mucus containing active *E. histolytica* were found in the stools. On emetine and quinoxy treatment he made a most remarkable recovery, and regained 44 lb in seven weeks. He was still in good health six years after his recovery.

An officer returned from Iraq in 1920 and suffered from amœbic dysentery with characteristic amœbæ and cysts in the stools. While under observation he had an attack of hepatic amœbiasis with a temperature of 103° F. Ten days after the subsidence of these symptoms, typical sprue developed with a sore tongue. For this he was treated on dietetic lines and made a good recovery. Since that time he has suffered from a sprue relapse after twenty years of apparent good health.

There is no doubt, also, that the affection known in India as hill diarrhoea\* (p. 402) may mark the onset of true sprue. In the author's series of two hundred consecutive cases there are five in which the dramatic onset of hill diarrhoea merged gradually into sprue —

An officer aged fifty six had spent thirty six years in India. In 1917, on the North Western Frontier, he had recurrent attacks of hill diarrhoea which ceased after persisting for four months. Three years later in 1920, true sprue symptoms with typical mouth and tongue lesions commenced. When seen in 1926 six years later, he was a typical case of sprue.

A man aged fifty had spent twenty one years on the railways in Burma

\* Whether these figures are in excess of the normal incidence of amœbiasis in tropical residents is a moot point. From such investigations as the author has been able to undertake, it is about the average.

While on a hill station in 1923, he suffered from hill diarrhœa. In 1924, true sprue symptoms began and ran a very rapid course. He was admitted to hospital in London in April, 1925, and died three and a half days later from typical sprue anæmia.

*Unhealthy surroundings*—There exists a popular idea in Ceylon and in the Far East generally that sprue originates only in those houses which have been attacked by dry rot. These are notoriously unhealthy and the inhabitants liable to catarrh of the nose, air passages, and intestinal tract. The soft timbers are invaded by white ants, or termites, and the faeces of these insects give rise to a fine dust which permeates the atmosphere. The author investigated this problem during his work in Ceylon in 1912-14, but concluded that there was not sufficient evidence to connect the dry rot with the regional incidence of the disease in that island. The subject has been revived by F. P. Jepson (1933), who has brought forward further evidence of the apparent connexion between the activities of dry-wood-inhabiting termites and the incidence of sprue, but there the matter ends, because the author has investigated many cases in seamen where the disease has originated on ship board and in other places where nothing of the sort can occur.

*Micro organisms*—For the last thirty years search has been made for some micro organism which might be the causative factor of the disease. Most theories have centred round the possibility of the infection of the intestinal tract by a yeast fungus. In 1901 a yeast was described by Kohlbrugge as the possible cause.

Kohlbrugge (1901) found in the intestinal mucus in the lymphoid patches of the intestinal canal, and in the epithelial covering of the tongue and œsophagus, large numbers of yeast cells resembling *Oidium albicans*, and these organisms were demonstrable in the faeces of sprue patients.

In Ceylon (1913) the author found that yeasts could be cultivated from the majority of sprue stools and saliva, and that in the acute, as well as in the terminal stages of sprue, they are the most prevalent organisms in the tongue lesions and in the stools. By using all the methods of differentiation then known he was unable to separate the yeast found in sprue from *Oidium albicans* as a distinct pathogenic species.

The prolonged researches of B. K. Ashford into the possibility of special species of yeast fungus being the causative factor have been inconclusive.

Biochemical investigations and their significance, which will be described later, have suggested to N. H. Fairley and others that the phenomena of sprue can best be explained in terms of a metabolic breakdown of the gastro-intestinal tract, characterized by defective absorption in the small intestine in some way connected with defective secretion of Castle's intrinsic factor by the pyloric or Brunner's glands. It may well be that the process is somewhat similar to that which occurs in hill diarrhœa under conditions of low barometric pressure and high humidity.

*Dietetic deficiency theory*—R. McCarrison suggested that sprue might



be a diet deficiency disease. In 1908 Carnegie Brown made the observation that in endemic regions native races are subject to beriberi and Europeans to sprue, and Elders (1917) postulated that sprue was a deficiency disease. L. Nicholls (1919) supported this hypothesis, and considered that a predisposing dietetic factor was important in the pathogenesis but that the essential mechanism was a lowered resistance followed by infection. Castle, Heath and Strauss (1931) and Castle and Rhoads (1932) appear to have confirmed that deficient diets frequently antedate the onset of clinical sprue.

*The author's theories*—Tropical sprue appears to have a definite geographical distribution and throughout its range it appears that the newcomer (i.e., the European) is attacked while the indigenous natives for the most part escape. Sprue moreover, appears to have an incubation period—that is to say its manifestations do not unfold themselves until after three to six months residence in the endemic area. This might suggest some specific communicable infection but on the other hand it is difficult to reconcile this theory with all observed facts—for instance the well established observation that the disease may commence in individuals who have quitted the endemic area and have lived in Europe for twenty five or even thirty years. It does not moreover, explain the prolonged latent or quiescent periods.

The clinical phenomena do certainly suggest a specific inflammation ranging throughout the intestinal tract and affecting the processes of assimilation—but biochemical researches indicate an affinity, or link with other allied diseases such as idiopathic steatorrhœa, cœliac disease, pellagra and pernicious anæmia.

In order that a proper conception should be obtained of the many factors possibly involved in the production of the sprue syndrome it is necessary to append a statement of the facts which have led up to the present attitude of mind.

In addition to the vitamins which have already been referred to (p. 329) other factors have to be taken into consideration.

*Extrinsic and intrinsic factors*—In order that normal hæmopoiesis may take place in the bone marrow it is necessary that it should be supplied with the hæmatinic or P.A. factor which is probably stored in the liver and in turn is produced by the interaction of an intrinsic factor normally present in gastric juice with an extrinsic factor. The latter is present in food and is closely related to vitamin B<sub>12</sub> but L. J. Harris states that though it has a distribution and heat stability remarkably like that of the vitamin complex it is distinct from riboflavin and nicotinic acid.

The extrinsic factor is contained in yeast preparations such as marmite, which is efficient in the treatment of the megalocytic hyperchromic anæmias of tropical sprue and idiopathic steatorrhœa but ineffective in the similar anæmia of pernicious anæmia so that it has been suggested that the anæmias which react to marmite and other yeast preparations are due to lack of the extrinsic factor. In this

connexion Miller and Rhoads have produced pernicious anemia in pigs characterized by megalocytic anemia lesions of the buccal mucosa, achlorhydria and absence of the intrinsic factor in the gastric juice on a diet which produces black tongue (or pellagra) in dogs and were able to cure them by oral and parenteral administration of liver extract

The intrinsic factor of Castle contained in the normal gastric juice of man is thought to be in the nature of an enzyme Meulengracht (1935) has shown that in the pig's stomach at any rate it is secreted by the pyloric gastric glands and the Brunner glands of the duodenum

*The response of glossitis and stomatitis of vitamin B<sub>2</sub> deficiencies to nicotinic acid and riboflavin*—The clinical appearances of the pellagrous tongue with marginal excoriations at the angles of the mouth are the same in the naturally occurring diet produced disease and in secondary alcoholic cases described by Spies Bean and Stone (1936) There appear to be no features which serve to differentiate it from a disease known as *endemic glossitis* in the absence of other accompaniments of pellagra described by the writer in Ceylon (Bahr 1915) and later by Nicholls and Nimalunja A similar glossitis has been found in ill nourished peoples in Palestine Central Africa India China West Indies and south United States

It has now become widely recognized that this form of nutritional glossitis and stomatitis is amenable to nicotinic acid and riboflavin therapy It is probably a pre pellagrous condition or larval pellagra comparable with the similar state in sprue which should hence forward be known as presprue or larval sprue (*see p 331*) The author believes that avitaminosis B<sub>2</sub> glossitis is not solely confined to those countries in which nutritional defects are universal and obvious but may also be encountered in Great Britain It is for instance by no means uncommon in patients suffering from intestinal disturbances and undergoing dietetic restrictions under medical direction and these cases are rapidly cured by nicotinic acid and riboflavin

*The connection between the glossitis and anemia of pernicious anemia tropical sprue and other steatorrheas and pellagra*—The glossitis which accompanied pernicious anemia closely resembles that of tropical sprue and pellagra According to Wilkinson Castle and Minot (1936) soreness of the tongue is found in 61 per cent of pernicious anemia cases which approximates to the figure of 75 per cent of the incidence of glossitis in tropical sprue Certain cases of pernicious anemia closely resemble tropical sprue The characteristics of the anemia are practically identical moreover achlorhydria and achylia gastrica which are cardinal features of pernicious anemia do not always afford an absolutely reliable means of differentiation for they may not be uncommon in tropical sprue But in the latter the absence or otherwise of acid in the gastric juice does not seem to affect the subsequent course of the disease Therefore in sprue the acidity of the gastric juice cannot be correlated to the absence of the intrinsic factor But in pernicious anemia this dysfunction is complete and permanent necessitating con

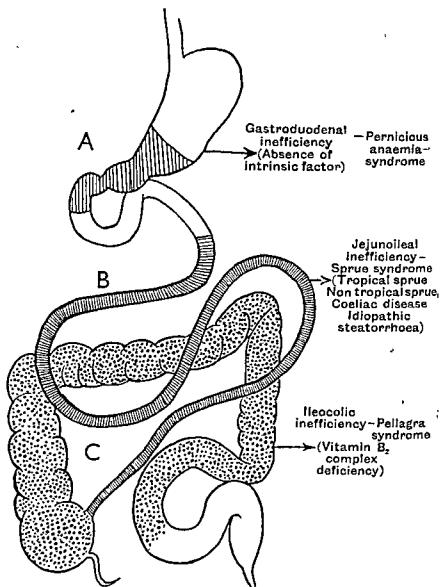


Fig. 59.

tinuous replacement of the intrinsic factor to maintain health, in tropical sprue it is apparently temporary, so that complete cure is frequently observed without continuous replacement.

It is generally accepted that the cells of the stomach and duodenum in pernicious anæmia may, though apparently intact, fail in their physiological functions and it is possible that a similar process may take place in tracts of the small intestine in tropical sprue.

The geographical distribution of pernicious anæmia in relation to that of tropical sprue appears to suggest the nature and ætiology of these diseases. Pernicious anæmia is extremely rare if not absent, in indigenous natives. De Langen and Lichtenstein (1936) have stated that in Java they have never found a case. Davidson and Gulland assert that pernicious anæmia is never seen in full blooded negroes and, according to the author's experiences the disease is rare in Europeans in the tropics.

The curative effect of nicotinic acid and riboflavin therapy upon the glossitis and stomatitis of pernicious anæmia is comparable to that observed in sprue and pellagra (see pp 335). There appears, therefore, to be some justification for pursuing the correlation of this group of diseases still further and for considering a close connexion between pellagra and sprue. Both may occur together in the same patient as C. G. Manning (1909) originally suggested.

As far as is known the geographical distribution of idiopathic steatorrhœa corresponds to that of pernicious anæmia and is mostly in the northern hemisphere. This disease is also characterized by glossitis which is similar to that of sprue and is also amenable to nicotinic acid therapy though other manifestations do not respond so favourably as in tropical sprue.

There appear to be some valid grounds at present for assuming some interconnecting link or common factor bridging the clinical appearances which separate this group of diseases: pellagra, pernicious anæmia, tropical sprue and other steatorrhœas. It is possible that the glossitis is non specific and common to this group and, as it has been shown to be due to a deficiency it is justifiable to postulate that this common factor is vitamin B<sub>1</sub>. There are now solid clinical, biochemical, pathological and comparative grounds for believing that in tropical sprue and the allied steatorrhœas the essential lesion lies in the small intestine and this idea has been fostered and stimulated by the suggestions of Bennett and Hardwick who have shown that the sprue syndrome is none other than the result of 'chronic jejuno ileal insufficiency', and thus it may be evoked by a number of diverse surgical and medical conditions. (Fig 59).

The main argument in this direction lies in observations made on gastro jejuno colic fistula which reproduces the main clinical and biochemical manifestations of tropical sprue, the same effects may occasionally be observed as the result of ill functioning gastro jejunostomy with short circuit. Other well marked diseases of the small intestine which may also produce the same end results are ulceration of the ileum,

blockage of the chyle vessels, as in lymphadenoma, tabes mesenterica or sarcoma of the mesenteric glands

It therefore appears justifiable to attempt to fit in these scattered observations in the light of recent developments and to postulate, on the basis of clinically observed results of surgical interference upon the gastro intestinal tract, that the essential lesion involves a particular part of the gastro intestinal tract

These views have recently received remarkable confirmation from a publication by N. Markoff, wherein it is stated that in two cases in Switzerland typical sprue syndrome supervened six months after 15 m. of ileum had been removed (ileocaecal resection with ileo transverse colostomy)

It is therefore inferred that the main signs and symptoms of sprue may be due to deficient absorption of vitamin B<sub>2</sub> (nicotinic acid) and thus appears to be borne out by the results of treatment (p. 338). As has been pointed out, in pellagra the symptoms may be produced, not so much by the lack of vitamin B<sub>2</sub> as by the failure to absorb it (J. R. Marrack). On the other hand, there are other vital physiological considerations which have recently come to light and which have a bearing on this problem. The presence of vitamin B<sub>2</sub> may be necessary for the proper absorption of fats by the villi (p. 350), or again, nicotinic acid therapy may act by producing a histamine effect and consequent increased flow of gastric and intestinal secretions, or it may be the direct action of histamine upon the villus. There are also Verzár's important observations upon adrenalin inefficiency in the production of steatorrhœa (see p. 353).

**Geographical distribution**—Tropical sprue is pre eminently a disease of the European, and is therefore found most widely distributed in those tropical localities where most Europeans congregate. It is essentially a disease of India and the Far East, though comparatively common in non tropical regions. The continent of Africa, especially the tropical region, has afforded very few authentic cases, but in 1928 the author described an indigenous case in a young European from Nyasaland. The explanation of this apparent anomaly of the distribution of sprue is not at present forthcoming. It seems certain that no known tropical disease can be the only predisposing cause.

In Asia, sprue occurs in India, Burma, Siam, the Malay States, the Straits Settlements, Cochinchina, China, Japan, Java, Sumatra, Celebes, Macassar, Borneo, Ceylon, and the Philippines, and the author has treated two cases from Mauritius. It has been recorded from Queensland, and the Northern Territories of Australia, and a few cases have been reported from Fiji. Sprue has been found in Russian Turkestan, Palestine, Mecca, Iraq, Egypt, and Malta. In the New World it is seen in the southern United States and is common in the island of Porto Rico, less so in Haiti and other West Indian islands, it has been reported from Mexico, Costa Rica, Panama, Venezuela, and

northern Brazil, and appears to be comparatively common in Dutch and British Guiana

Recently, much interest has been aroused by the recognition of a sprue like disease in Denmark and Scandinavia generally, which has been designated by Thaysen (1932) 'non tropical sprue' (see p 847) which appears to be closely connected with tropical sprue

*Sprue cases seen in native races*—Van der Burg (1880) recognized sprue in Javanese, Malays, and negroes, he considered the lighter coloured Chinese to be more frequently attacked than members of the darker skinned races, but only after prolonged residence in an endemic area. He mentioned that after thirty years' residence in Java he had only been able to recognize thirty two cases in natives

Jeffreys and Maxwell, in 'The Diseases of China,' described a typical case of the disease in a Chinaman, and Ashford (1913) in natives of Porto Rico and the Antilles

During the author's work in Ceylon in 1912-14 notes were collected of eleven definitely diagnosed cases in natives. Five were recognized immediately before death. It was established that the disease occurred, though rarely, in members of several races—in Moors, Sinhalese, Indians, and Tamils who had been bred and reared in Ceylon. During the last twenty one years in London five cases have been seen and treated, mostly in the educated and cultured class of Indians. The author has never seen sprue in any member of the negro race

In June, 1929, an Indian lady aged forty was seen, she had suffered from sprue symptoms for twelve years. She presented then a typical picture of the disease, with severe anæmia, emaciation, distended abdomen, sore tongue and typical stools, together with œdema of the feet. Admitted to hospital she was treated with success by high protein dietary and liver injections. Seen again in May, 1937, she appeared to be in excellent health, having gained in all 63 lb in weight

In May, 1925, a prominent Indian of twenty three years of age was seen and treated. He had contracted the disease in the neighbourhood of Bombay in 1924, and had been steadily losing weight, then weighing only six stone. The diarrhœa, anæmia, sore tongue, and stools were all typical. He was by no means an easy man to diet or to treat, but despite many difficulties, he had made a good recovery by September of that year. Seen again six years later, in 1931, the author was able to verify that he had made a permanent and good recovery, though he had been back to India in the interval. He then showed no signs whatever of anæmia or sprue, and his weight had increased to 9 stone 1 lb, or by 43 lb

In hospital practice the author has had experience of two cases of undoubted sprue in native seamen from the P and O Line. The first was seen in 1922, is a Lascar of twenty five years of age. He had the typical tongue, diarrhœa, and emaciation, with anæmia and had been previously diagnosed as a case of scurvy. Under appropriate treatment his weight increased by 10 lb in five weeks. The second was also a Lascar, aged thirty, who was seen in January, 1935. In this case also all signs and symptoms were typical of sprue and abated on appropriate dietetic treatment

**Epidemiology and endemiology**—The epidemiological facts so far collected go to show that sprue is a regional, as opposed to a climatic disease, for it is known in localities as climatically distinct as Java and Tientsin in central China. Atmospheric temperature alone does not seem to influence its incidence, for it may originate in high altitudes in Ceylon and in the Himalayas above 6,000 feet where the climate resembles that of Europe. Its occasional occurrence in central Arabia, where the atmosphere is essentially a very dry one, runs counter to the view that a damp climate is a necessary factor in its causation. On the whole tropical sprue appears to extend for twenty degrees further north than it does south of the Equator (i.e. 40°N, and 20°S).

*Incidence of the disease in its endemic zones*—Sprue is more likely to attack the lighter skinned races—Europeans first Chinese and Japanese second, Malays third, dark skinned Hindus and Tamils very rarely, in the highly pigmented negroes it appears to be excessively rare. On the whole too, it may be said that the more highly civilized peoples are attacked more than those less sophisticated. The disease is apt to occur in one or more members of the same family—the author has recorded instances of sprue in both husband and wife. Moreover, there is a tendency for it to occur more commonly in one particular house, the terms 'sprue houses' or 'sprue bungalows' being applied in Ceylon.

As a rule, sprue attacks those of middle age especially Europeans who have been resident for several years in the endemic zone of the disease. Among them when the numbers of both sexes are equal, the female appears to be slightly more liable than the male. The author is convinced that the disease rarely occurs in small children—he has seen only two instances of sprue under twenty years of age in boys of thirteen and eighteen respectively. In 1933 R. H. Miller demonstrated at the Royal Society of Medicine an undoubted case of sprue in a boy of 11½ years of age from Ceylon.

Another peculiarity of sprue is its latency. Whatever the cause may be, it can remain latent in the body, without provoking any symptoms, for as long as fourteen to thirty seven years. Sometimes it manifests itself after so long a period that the practitioner is at a loss to associate the train of symptoms with previous residence in the tropics. Two instances may be cited—

A medical practitioner, aged seventy two returned to England after thirty years residence in China. Symptoms commenced when he had been in England fourteen years. Typical ulceration of the tongue and mouth, with diarrhoea of persistent type very marked anaemia excessive loss of weight and dry inelastic skin were noted. Recovery was complete after blood transfusion and dietetic treatment.

In 1927 the author was consulted by a lady of fifty seven who had lived in India continuously up to the age of thirty seven. The disease manifested itself in the classical manner by severe early morning diarrhoea with copious frothy, offensive stools, tongue symptoms and dysphagia appeared later. She died of sprue eight years after the onset of symptoms. Others have been encountered where the interval was 25, 30 and 37 years.

There has been some doubt concerning the length of time which must elapse, after residence in the tropics, before the development of sprue symptoms. Formerly it was thought to be a period of years, but evidence has been collected which shows that it may be as short a time as three months, for visitors to Ceylon and India and the Dutch East Indies, who have been there for only a few months during the winter season, and who have never previously resided in the tropics, have returned to England with definite symptoms. Two cases may be cited —

The first is that of a boy aged eighteen. Symptoms of sprue commenced five months after arrival in Java, with gradual onset of diarrhœa, typical stools, and sore mouth and tongue. The total loss of weight was 35 lb., there was complete recovery on appropriate treatment.

The second case is that of a woman aged fifty-seven. Symptoms of sprue with sore mouth and dysphagia commenced after three months' residence in Ceylon, during her first visit to the tropics. Diarrhœa with typical stools and loss of weight followed later, and persisted for six months after her return to England.

During the author's studies on sprue in Ceylon in 1912 and 1913, records were obtained of two cases in which the disease began respectively six weeks and three months after the patient's arrival in that island.

*Sprue contracted at sea* — In 1927 the author had under his care a captain of the P & O Line, aged 54. Symptoms of sprue commenced at sea in 1926 when he was fourteen days out from Bombay. He had the typical syndrome of sore tongue, aphthous stomatitis, diarrhœa, and anæmia. There was little or no evidence that residence ashore had had anything to do with the onset of the disease. He had been at sea for forty years, sailing to India and Australia, and during that period he had never spent more than one night ashore in Bombay or any other Indian port. He was treated in May, 1927, and reacted very well to dietetic and liver treatment. Four months afterwards he returned to sea, but did not suffer any further from sprue symptoms.

In searching through his hospital records the author has found no less than ten cases in which the first symptoms commenced at sea. All occurred in officers (engineers and seafarers), employed by the P & O or B I Lines running to India and the Far East. Their ages ranged from 29 to 51 years. All apparently did well under treatment, but two came for further treatment of relapses.

*Non tropical sprue* — The most important contribution to this subject is undoubtedly the monograph by Hess Thaysen in 1932. There the pathogenesis of tropical sprue, idiopathic steatorrhœa and coeliac disease in children is studied in great detail. After considerable discussion he supports the view that the three complexes—sprue, idiopathic steatorrhœa and coeliac disease (Gee Herter)—should be grouped together as 'the coeliac affection'. His views have not received



universal support and the gist of the matter now appears to be that the following clinical states can be recognized —

- 1 Cœliac disease in children a congenital condition
- 2 Idiopathic steatorrhœa of adults which probably results from previous cœliac disease in infancy and which is accompanied by multiple skeletal changes
- 3 Non tropical sprue a sprue like disease occurring rarely in temperate and northern countries which is amenable to the same methods of treatment as is tropical sprue
- 4 True tropical sprue the type disease originating in tropical and subtropical countries

The literature on this subject has now become voluminous and as may be expected from the intricacies as well as from the close similarity of the complexes concerned the issues have become confused. The author is now convinced from his personal experience that very occasionally cases resembling true tropical sprue with glossitis steatorrhœa and anæmia may be met with in England and respond to the same methods of treatment in the same manner as tropical sprue. He has records of three such cases. The first described (1939) as non tropical or indigenous sprue was in a woman of 28 years of age who had never been out of England. The stools glossitis emaciation and anæmia were typical. She suffered from three relapses and eventually recovered on dietetic treatment. Two others were recorded (1940) and responded to nicotinic acid therapy. One was in a Pole of 56 who had resided in London for 42 years the third in a man of 64 who had suffered from recurrent glossitis and stomatitis with steatorrhœa and anæmia for eight years and who had only once been out of England to Egypt fifteen years previously. Bennett and Hardwick (1940) have also recorded two cases which seem to fall into the same category. In none of these were there any bone or skeletal changes and the general facies of the disease was identical with that of tropical sprue.

#### PATHOLOGY AND PATHOLOGICAL ANATOMY OF SPRUE

In patients dying after such a prolonged chronic wasting illness the pathological changes observed are usually the results of atrophy and thus do not give a picture of the actual primary lesions. For this reason pathological studies have so far failed to elucidate the actual ætiology of the disease any further though they have to some extent assisted in the differentiation of sprue from pernicious anæmia cœliac disease idiopathic steatorrhœa etc.

In chronic sprue the tissues are abnormally dry owing to dehydration the subcutaneous and visceral fat almost absent and there is general muscular wasting. The internal viscera also are shrunken. The liver for instance is reduced to almost half its normal size while the spleen and adrenals are reduced to nearly the same degree. The pancreas has been described as fibrotic though the islands of Langerhans

remain intact Somewhat similar fibrotic changes are found in the liver and kidneys

The heart is usually small and in a state of brown atrophy In the author's series of cases (1912) it weighed less than four ounces while F P Mackie and N H Fairley (1929) found that in one of their cases it was only 2½ ounces they consider this change specific and the reduction in weight out of all proportion to any decrease explicable in terms of starvation

Naturally attention has been focused upon the intestinal tract and it appears that as more detailed information is obtained many of the appearances which have been described as essentially sprue lesions are due either to post mortem changes or to secondary infections which are likely to occur in such a chronic and protracted disease Knowledge on this subject has been amplified by the studies of Thaysen (1931)

The tongue shows desquamation of the epithelial layer and especially on the surface of the fungiform papillæ

The bowel especially the small intestine has been described as being so attenuated as to be diaphanous The stomach is normal in appearance though in the autopsies the author has performed it was found that the mucous surface was plastered with mucus The chief lesions observable in the intestines especially in the ileum are thinning and atrophy of the mucous membrane with degeneration of the absorptive and secretory epithelium Mackie Fairley and Thaysen maintain the view that these minor changes are essentially due to degeneration and aplasia and that the inflammatory changes described by the author and others are due to accidental changes in the general course of the disease They have found evidences of blood destruction in the mucosa suggesting the absorption of some hæmolytic substance in the intestines and the destruction of blood *in situ* The author also has described the presence of blood pigment and its by products in the small intestine

The internal surface of the bowel is usually coated with a layer of thick mucus and occasionally superficial ulceration and pigmented scars of previous lesions have been observed Death from perforating ulcers has been described by Faber (1904) Fischer and von Hecker (1922) and the author (1924) while Carmichael Low and N H Fairley (1934) have reported a fatal case from perforation of the cæcum due to thrombosis of a vein It is now generally admitted that ulceration of the small intestine may be regarded as a secondary phenomenon

Although atrophic changes are more marked in the lower end of the ileum they may occur in a patchy manner throughout the large intestine and diaphanous patches can be demonstrated by sigmoidoscopy It is possible that the inflammatory appearances of the tongue and mouth and indeed of the whole alimentary tract are evanescent and so being visible only in the acute stage of the disease cannot be demonstrated post mortem Further information on this point can only be obtained by actual and systematic observations of the mucous membranes during life

It may be that the pathological changes in the upper intestinal tract, insignificant though they are to the eye, are of such a character as to inhibit the secretion of the intrinsic factor, and thus be responsible for the macrocytic anaemia of sprue. Mackie and Fairley have for this reason, paid especial attention to the bone marrow changes. The red marrow is much reduced in quantity though in two cases they found hyperplasia similar to that of pernicious anaemia. Their findings suggest that in sprue there is a toxin which primarily stimulates, and later leads to exhaustion of the hæmopoietic function, so that in the terminal stages complete aplasia results.

These pathological studies go to show that sprue is a specific disease of the intestinal tract which leads to progressive degeneration of the absorptive and secretory tissues and to slow and progressive starvation.

**Histopathology**—In the microscopic pathology there are very few points of real importance. In sections of the tongue desquamation of the stratified epithelium especially of the fungiform papillæ can be demonstrated. The same changes are visible in the œsophagus but often the pathological appearances may be obscured by a down growth of yeast fungi (*Oidium*) now regarded as being secondary invaders.

The structure of the stomach membrane may be normal but the intestinal canal from duodenum to rectum usually exhibits chronic inflammatory changes. In the ileum the villi are quadrangular and shrunken. The cells stain badly and the goblet cells are distended with mucous secretion. Chronic inflammatory changes are evident in the congestion of the capillaries and the infiltration of the interglandular tissue with lymphocytes and plasma cells. There are similar subacute inflammatory changes in the submucosa and extensive fibrous changes in the muscular coats. (Fig. 60)

Sections of the liver show extensive fatty changes in the cells at the periphery of the lobules and deposition of hæmosiderin granules. The spleen is never enlarged but shows a deposition of pigment in the pulp cells and hyaline changes in the endothelium of the venous sinuses. This hyaline degeneration manifests itself by the presence of numerous droplets of hyalin which stain with Weigert and are known as Russell's bodies. Similar changes have been seen in the tongue the mucous membrane of the intestinal canal and even in the lymphatic glands and bone marrow. The changes in the bone marrow cells vary according to the degree of anaemia present and are well described by F. P. Mackie and N. H. Fairley (1929).

#### CLINICAL PATHOLOGY OF SPRUE

**Stools**—The important features of sprue stools are their colour, size, and chemical composition.

**Colour**—It was formerly considered that the large frothy stools

owed their lack of colour to the reduction or total absence of bile pigments it is now known however, that bile pigments are present in normal amounts but their colouring is masked by an abnormal amount of fat. If the almost colourless sprue stool is extracted with 90 per cent alcohol and the filtrate is exposed to the air colourless fluid results which slowly takes on the yellow colour of hydrobilirubin. That the normal amount of bile is excreted into the gall bladder is evident from the abundant amber coloured bile found post mortem.

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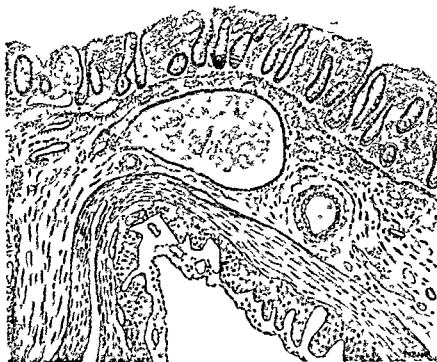


Fig. 60—Section of the ileum in sprue showing general atrophic changes and round cell infiltration of the mucosa.

**Size**—The large size of the stool has been variously commented upon but it naturally depends upon the amount of undigested food residue. The average daily weight of a normal stool when the patient is taking a pure mill dietary is estimated at 6 ounces (170 grammes) according to most authorities 80 per cent of the solid matter ingested in the food is normally absorbed. The size of the sprue stools varies enormously in the author's experience the largest amount passed in one day weighed 72 ounces (after an injection of pitressin). Analysis of

these stools goes to show that less than 60 per cent of the solid matter is absorbed (Fig 61)

*Chemical composition*—A great amount of excess fat is passed in the stools and *pari passu* with this there is a correspondingly low fat content of the blood (112.8 mgm per cent against the normal 600 mgm) N. H. Fairley finds that in 80 per cent of his cases the total fat in the dried faeces at a single examination exceeded 25 per cent but after recovery the faecal fat returns to normal limits. In severe cases of



Fig 61—Appearance of typical sprue stool in glass container

sprue over 50 grammes of fat is not uncommonly excreted when the patient is on a mixed dietary. In sprue stools the fats are split by the action of the pancreatic and intestinal juices but the split fat is not absorbed so that the proportion of fatty acids to neutral fats may be as high as five to one. In pancreatic disease on the other hand the neutral fats predominate over the fatty acids and may be fifteen times as great. These figures seem to indicate that in sprue the pancreatic digestion proceeds normally but that the products of this digestion are not properly absorbed. The reaction of the sprue stools is almost invariably acid this is due to the amount of fatty acids a fact which accounts for the peculiar sour and penetrating odour.

The interesting fact that bile pigments are present in normal amounts shows that a deficiency of bile cannot be the cause of the malabsorption of fat. Yet that there is malabsorption is shown by the great amount of split fat in the stools and in clinical practice, in the author's experience the administration of bile and bile salts to sprue patients invariably aggravates diarrhœa. Malabsorption may be due to excessive motility

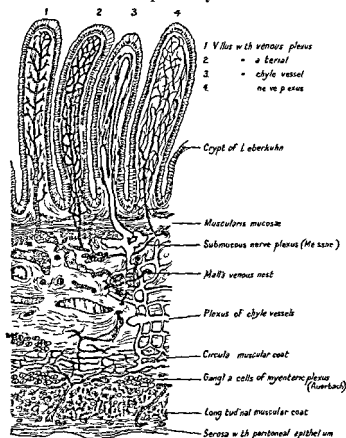


Fig. 62.—Section of ileum to show structure of villi

(Partly after J. Schaffer—*Verlesungen über Histologie* 1911)

(Modified by Verzar and McCullough 1936)

and peristalsis the intestinal contents being so hurried through the small intestine that they have no chance of being absorbed as appears to be the case in some instances of short circuit of the small intestine which may assume the clinical appearances of sprue. On the other hand the initial fault may lie in adrenal deficiency as in the original work of Verzar who, together with Laszt, has shown that absorption of glucose and flavin as well as conversion of provitamin B<sub>2</sub> into active lactoflavin-5-phosphoric acid depends upon normal adrenal action.

It has further been shown that the presence of vitamin B<sub>2</sub> (nicotinic acid and riboflavin) is necessary for normal fat absorption and that therefore there exists a definite connection between this vitamin and adrenal activity, and on this property probably depends disturbance of fat absorption in pellagra and possibly also in sprue, celiac disease and idiopathic steatorrhea. It is therefore apparent that physiological processes underlying fat absorption are more complicated than had formerly been supposed.

Steatorrhea can be brought about as a result of a break at any point of this physiological chain. Only future physiological and pathological investigation can determine where the cardinal lesion of sprue and allied diseases may be situated. It may be (1) in the adrenal cortex, (2) in inhibition of phosphorylation, (3) in absence of the duodenal hormone—*vitellin*—and consequent disordered function of the villi. Whatever may ultimately prove the correct mechanism it appears more than probable that vitamin B<sub>2</sub> plays an essential role in linking together these complicated processes.

**Other considerations in the physiology of the intestine**—Carbohydrate absorption is effected in an easily explicable manner. It is absorbed as monosaccharides but cane and milk sugar are inverted in the small intestine. The bulk of carbohydrate food consists of starch which when converted into maltose and dextrin is completely absorbed. After entering the portal vein dextrin is distributed first to the liver, where the excess is withdrawn and stored as glycogen. Carbohydrates which escape absorption are liable to acid fermentation from ever present bacteria, with the production of acetic and other acids.

Digested proteins are absorbed by the blood vessels of the villi and when in excess, they and the peptones are taken up by the lymphatics. Amino acids enter the blood as such without undergoing synthesis. Proteins which escape absorption are disintegrated by bacterial action and very little finally appears in the faeces.

In the large intestine the secretion is alkaline and is not characterized by destructive enzymes. Absorptive processes continue and there is a marked absorption of water while the alkalinity renders it favourable for bacterial action. The composition of faeces differs widely in amount and character according to the nature of the food. On a meat diet they are small and dark; on a mixed diet the amount is increased, and they are largest on a vegetable diet. The offensive odour is increased by excessive putrefaction. The average weight on a mixed dietary is 170 grm.

**The blood in sprue**—One of the most characteristic features of this disease is the great anaemia. To such an extent does blood destruction take place, that a parallel can only be found in severe exacerbation of true Addisonian (or pernicious) anaemia.

The conclusion arrived at by many workers is that a grave degree of anaemia is found in the most advanced stages of the disease. In the

early stages there is no alteration in the number of red or white cells or in their relative proportions, as the disease progresses, however, the former become profoundly altered both in shape and size, and nucleated red cells may appear, though this is rare. On the whole the blood picture of the fully-developed sprue case is that of megalocytic anaemia, and the colour index in the majority of cases is above 1.

There appears to be little evidence for regarding the anaemia of sprue as other than secondary, probably due to the non absorption of the hæmatopoietic factor from the diseased intestinal canal or to the absence of the intrinsic factor from the achlorhydric stomach. In all probability both these factors are involved, but the latter is more important. The very variable degree of anaemia found in cases of this disease coincides with the variable appearances of the bone marrow. Studies on the blood in sprue have been carried out by G. C. Low, by the author together with H. B. Newham and R. V. Morris, and more recently by N. H. Fairley, F. P. Mackie, and H. S. Billimoria (1929). The conclusions of the last named workers are as follows —

At the onset anaemia in sprue is rarely found to be so severe as that encountered at a corresponding stage in pernicious anaemia, and during the subsequent course of the disease a grave stage of anaemia less frequently develops. As a general rule, grave anaemia occurs with greatest frequency in patients over fifty years of age. In about 17 per cent of cases red cell counts of under 2,000,000 were noted. Exceptional cases of 575,000 and 400,000 red cells per cmm are recorded. Throughout all the stages of the disease 61 per cent of cases showed a colour index equal to or exceeding unity while in the remainder values from 0.9 to 0.99 were found, in no instance was it less than 0.8. The blood picture remains remarkably constant, and anisocytosis is an outstanding feature, especially as regards the increase in size. Microcytes are less in evidence than are the larger form of red blood cells, while poikilocytosis and polychromasia occur but to nothing like the degree usually observed in pernicious anaemia. As in the author's experience, nucleated red cells are rarely seen.

In uncomplicated sprue, the leucocyte count is either normal or there is a leucopenia usually associated with a relative lymphocytosis. A leucocytosis, indicating some intercurrent infection, was observed in only five cases.

A blood crisis in sprue is characterized by a rapid and critical fall in both the hæmoglobin and the red blood corpuscles, this condition is generally associated with severe diarrhoea and progresses to a fatal issue without remission, and without those evidences of corpuscular regeneration which constitute the typical picture of similar crises in pernicious anaemia. The Price Jones curves investigated in eleven cases resembled those obtained in true pernicious anaemia, being characterized by marked asymmetry, broadening of the bases, displacement to the right, and a definite increase in the mean diameter of the corpuscles to  $8.07\mu$ , so that essentially the anaemia is of the megalocytic



type The Van den Bergh reaction showed a mean value of 0.66 unit. A comparison between these results and those obtained in cases of malaria and acute pernicious anaemia shows that hyperbilirubinæmia is found more frequently in the two latter diseases, thus the data afforded by this reaction are often of considerable value in differentiating sprue from true pernicious anaemia.

As a result of these investigations it seems that deficient blood production rather than excessive blood loss constitutes the basis of sprue anaemia. The trouble appears to start in an ill nourished bone marrow which poisoned by toxin derived from the alimentary canal, undergoes primary hypertrophy and secondary atrophy.

*Serum calcium and phosphorus content*—The association of tetany with the chronic diarrhoea of sprue—and in fact, with other forms of chronic diarrhoea—suggests that there is a calcium deficiency. H. H. Scott in 1923 focused attention on the deranged calcium metabolism in this disease, and in 1925 pointed out the value of estimating the serum calcium in sprue both for purposes of diagnosis and as a gauge of treatment.

N. H. Fairley, F. P. Mackie and F. J. Sacasa (1926) confirmed Scott's observations that the ionic calcium was lowered in sprue readings 7.4–9 mgm per 100 c.c. of serum being constantly registered. E. A. Baumgartner (1927) found in cases of tetany that the total calcium was decreased, readings of 3.1 mgm to 6.2 mgm per 100 c.c. of serum being recorded in such cases. G. C. Linder and T. F. Hanes (1930) found that low calcium values (7.3 mgm–7.5 mgm) were associated with a lowered serum phosphorus content (2 mgm per 100 c.c.), and that when a low fat diet was instituted the tetany disappeared and the serum chemistry became normal.

In 1930 N. H. Fairley investigated this subject again using Kramer and Tisdall's technique for calcium and the inorganic phosphorus method by Brigg's modification of Bell and Doisey (1922). In twenty-one cases the average value of calcium was 8.8 mgm per 100 c.c. The total serum calcium may be regarded by this method as being normally 9.1–11 mgm per 100 c.c. In cases with tetany it varies from 5 to 7 mgm per 100 c.c. The average blood phosphorus reading was 3.2 mgm per 100 c.c. of serum, thus, since in normal people the inorganic phosphorus usually varies from 2 to 4 mgm per 100 c.c., no rise above the normal was noted in this series. This finding precludes a parathyroid deficiency as the basis of the hypocalcæmia.

As a result it is concluded that defective absorption is the basic factor involved in the low calcium content, and that in these circumstances a low fat dietary, calcium salts, and irradiated ergosterol are indicated.

*Blood sugar regulation*—In 1926 Thaysen pointed out that in sprue there is an abnormally low blood sugar curve, a feature common also to coeliac disease (Gee Herter disease) and other idiopathic steatorrheas.

(Gee-Thaysen disease) In these curves the blood sugar does not rise above 40 mgm per 100 c c

The fasting blood sugar value varies a great deal, the lowest recorded by Thaysen was 62 mgm per 100 c c In 48 cases of sprue, Serra found an average fasting blood sugar value of 101 mgm per 100 c c, while Fairley and Mackie in 17 cases found 84.4 mgm per 100 c c These findings seem to indicate that the low blood sugar curve is not due to impairment of the glucose absorption or to destruction of glucose in the intestines through abnormal bacterial activity Thaysen considered that this type of curve is due to an abnormality in the function of the regulating mechanism which maintains the normal blood sugar concentration, an abnormality possibly due to the disordered function of the adrenal gland

Fairley's recent results (1936) show that in 42 out of 50 cases flat glucose curves can be demonstrated A new intravenous glucose test has been devised Ten cases of sprue thus investigated all showed high curves as compared with the normal, and a marked delay in the return to the fasting level On recovery from sprue the intravenous glucose curves were always found to be lower and to approximate closely to the normal This utilization of glucose is to be attributed to a decreased sensitivity to insulin It follows therefore that intravenous glucose and insulin are indicated in the treatment of gravely ill patients

*The blood cholesterol*—This subject has been investigated by H B Newham, R M Morris, and the author (1926) They pointed out that in all cases of sprue anæmia there was a definite hypocholesterolaemia which bore little relationship to the degree of anæmia present and they found that the constant low cholesterol content of the blood in pernicious anæmia could not be differentiated from that of sprue N H Fairley, in investigating the above series of sprue cases, found the serum cholesterol averaged only 72.8 mgm per 100 c c and that the lowest reading was 40 mgm Normally the serum cholesterol varies between 100 and 220 mgm per 100 c c The interesting feature of this investigation was that the serum cholesterol content rose rapidly on liver extract therapy and high protein diet

*The gastric secretion*—The fractional test meal analysis has been carried out by N H Fairley, F P Mackie, and their co workers in Bombay, and also by the first named in London The results have been variable For the most part there is either relative hypochlorhydria or a normal production of acid Out of forty four cases examined, fourteen showed complete and the remainder a relative achlorhydria, so that, without histamine, this test affords no information of definite value in differentiating sprue from pernicious anæmia The achlorhydria revealed by the fractional test meal is, however, by no means synonymous with achylia gastrica, therefore response to the administration of histamine was used as a method of differentiation In a series of cases  $\frac{1}{4}$ – $\frac{1}{2}$  mgm of histamine was injected during the pro

gress of the fractional test meal two hours after the gruel had been administered. In thirteen out of eighteen cases a definite secretory response was obtained, while in five there was a true achylia gastrica. It thus follows that gastric involvement in sprue undoubtedly results in a decreased acidity, although at the onset of the disease there may be hyperchlorhydria. In this respect the gastric secretion differs from that in true pernicious anæmia, with which disease, it is now universally accepted a true achylia gastrica is invariably associated. In the achylia of sprue histamine response may be regained after proper medicinal treatment. In his latest papers Fairley states that in 100 cases only 22 failed to secrete acid when histamine was injected.

In the author's series (1941) the after history shows a variable secretion of hydrochloric acid in the gastric juice and even achylia gastrica. Apparently the presence or absence of this acid bears no relation to prognosis.

A. R. Olleros (1940) has demonstrated in sprue atrophic gastritis somewhat resembling that of pernicious anæmia and more recently has extended his researches by employing chromoscopy or the elimination of neutral red from the mucosa. Though in general in hyporecidity this takes place more slowly than normal yet in sprue it is effected more rapidly than normal and it is said to afford a valuable means of differentiating between sprue and pernicious anæmia.

**The urine in sprue**—The urine excretion in sprue does not appear to have attracted much attention. According to the observations of the author (1915) the amount of urine passed *per diem* depends upon the presence of diarrhoea, as when this is acute the secretion of urine is diminished. The reaction appears to be invariably acid and the urea content normal. Interest is centred on the presence of indican and urobilin. Indican is present during the acute stages and apparently depends on the amount of intestinal putrefaction present. Urobilin appears intermittently in the urine especially when the diarrhoea is acute and when there is marked anæmia. Its presence depends on the degree of blood destruction.

**The diastatic reaction**—The diastatic reaction has been investigated by the author and H. Willoughby. The figures obtained varied from 20 to 29 diastatic units which is well within the normal limits. It is suggested that the diastatic reaction affords a means of differentiating sprue from chronic pancreatitis but this cannot be accepted without qualification. It is true that in acute and chronic pancreatitis the diastatic index of the plasma as well as of the urine is greatly increased and that such an increase may be taken to denote a pancreatic lesion. But, on the other hand, a normal diastatic index cannot be regarded as evidence that the pancreas is sound.

Recent investigations (unpublished) have shown that in acute relapses of the disease there is as in pellagra hyperporphyrinuria.

**The saliva in sprue**—The chemistry of the sprue saliva has been investigated by Van der Scheer (1906) and later by the author (1915).

The former found the saliva alkaline to litmus in the early stages but acid in the more advanced cases. The author found the reaction markedly acid to litmus paper especially in the advanced stages the acidity could most clearly be demonstrated on the surface of the tongue and over the inflamed fungiform papillæ. In normal subjects the saliva is alkaline or neutral.

**Summary**—The conclusions which may justifiably be drawn from these biochemical investigations point to the probability that unabsorbed glucose undergoes fermentation in the small intestine and that this is responsible for the intestinal fermentation and the gaseous acid features of sprue stools the unabsorbed fat accounting for their greasy and bulky characters. The calcium in the bowel unites with the excess of fatty acids to form insoluble calcium soaps and this together with decreased absorption is possibly the basis of the hypocalcæmia. It is certainly a fact that the treatment of tetany by oral calcium is ineffective until the fat content of the stools has been adequately reduced.

#### SYMPTOMATOLOGY OF SPRUE

In hardly any other disease is there such an infinite variety and combination of symptoms as in sprue. This applies to the appearance of the patient as well as to the progress of the disease. Sprue is really a symptom complex there are tongue and mouth symptoms abdominal symptoms emaciation anæmia and lastly the curious mental outlook that accompanies this disease. As J. Fayrer wrote in 1881 the appearance of persons suffering from this disease is characteristic. They are pale and emaciated with loose dry flaccid flabby skin which in later stages becomes discoloured as by chloroma or Addison's disease. The fat disappears the eyes are pearly the lips and conjunctiva are blanched the tongue is dry and smooth and in advanced stages it appears contracted and shrunk. There is at last extreme anæmia dropsical effusions take place into the areolar tissue and the lower extremities. In fact the appearance of sprue patients is so striking that those who are familiar with this disease can recognize it *d'un coup d'œil*. (Bertrand and Fontan.)

The cardinal symptoms are to be sought in the mouth the abdomen and the typical stools. It is necessary to emphasize that not all the signs and symptoms which are described in text books may be present in the same patient. Symptoms vary according to the region of the alimentary canal which is specially involved and this permits the method of classification of clinical appearances followed in this work. All cases exhibiting the characteristic tongue and abdominal symptoms and typical stools are designated as *complete or typical sprue*. In this category are included cases of all degrees of severity subdivided into mild acute and chronic. *Incomplete sprue* includes a large number of cases in which though the typical diarrhœa is present no abnormal pathological changes of tongue or buccal mucous membrane can be

distinguished but in some of these the typical tongue and mouth symptoms may become apparent as the disease progresses. It cannot be too strongly emphasized that there are rare cases of sprue which terminate fatally without the full picture of the disease being developed. A further subdivision in which the sprue process appears to be confined to the buccal cavity may be termed *larial sprue*. These cases are rare and when observed over a number of years the more dramatic abdominal symptoms may be found to supervene.



Fig. 63.—Facies of sprue showing the typical sprue glossitis

**Mouth lesions** (Plate XII 1 facing p. 378).—When the mouth of a typical sprue case is examined the soreness and tenderness will be found to depend upon a variety of lesions of the mucous membrane which appear to be very superficial (Fig. 63). It is characteristic that these lesions vary in intensity from day to day. During an exacerbation of the disease the tongue appears raw red and angry patches of congestion and minute vesicles appearing on its surface especially at the tip and sides in the later stages owing to swelling of the

mucous membrane, the tongue assumes a fissured appearance. It is remarkable how very quickly the filiform papillæ atrophy while the fungiform papillæ become apparent, standing out pink and swollen upon a polished background. On turning up the tongue similar patches of erosion are usually visible on the under surface, and aphthous looking pellicles can be seen on either side of the frænum linguae. Sometimes similar patches can be seen on the mucous membrane of the upper and lower lips, and frequently also on the buccal mucous membrane. The palate is very seldom affected. When it is the mucous follicles are seen to be enlarged and prominent. Occasionally the fauces and the uvula may be congested and red. In acute cases excoriation of the angles of the mouth (angular stomatitis) may be observed.

As a result of the irritation caused by these very sensitive lesions the mouth fills with a watery saliva which dribbles from the corners. Should the patient attempt to take any acid food, wine or fruit juice especially that of the orange or pineapple, the pain and burning are intolerable, eventually eating anything except the plainest diet becomes impossible. Swallowing is often accompanied by a sense of soreness and burning under the sternum. Dysphagia occurs in about 12 per cent of cases, this very disagreeable symptom being due to excoriation of the œsophagus, which apparently takes place in the same manner as in the mouth.\*

During exacerbations of the disease the condition of the tongue and mouth become greatly aggravated. It is not uncommon to find however, that the mouth signs precede the onset of diarrhœa, and that when the latter is well established amelioration of the mouth condition takes place. At all times during the progress of a sprue case the tongue is abnormally red and devoid of fur, the organ as a whole is swollen during the exacerbations but shrunken in remissions. In a small proportion of cases the tongue and mouth symptoms precede the onset of the diarrhœa. Occasionally (see p. 367), they may constitute the only indications of the disease.

The vesicles, or aphthæ, of sprue are characteristic and have to be distinguished from the aphthous ulceration seen in the mouth in other chronic conditions. These aphthæ are present in about 22.5 per cent of cases, they usually measure 1.2 mm. in diameter and appear to commence in the lower strata of the tongue epithelium as a vesicle which bursts and develops into small ulcers which are extremely sensitive and very evanescent. They have been seen on the inner margin of the lower lip and frænum linguae, at the tip and sides of the tongue and on the mucosa of the cheek opposite the lower molars,

\* The association of glossitis, anemia and dysphagia directs attention to the phenomenon known as the *Plummer Vinson syndrome* about which there has recently been discussion. This syndrome is practically confined to women and is associated with achlorhydria. There is difficulty in swallowing which is localized to the level of the larynx and is progressive. Œsophagoscopy usually reveals some stenosis. Probably this dysphagia is of different etiology to the dysphagia of sprue which is a sense of constriction confined to the lower portion of the œsophagus the pain being referred to the base of the sternum.

but never on the palate or the fauces. Tongue and mouth lesions were constantly present in about 70 per cent of cases in the author's series.

**Abdominal symptoms**—Dyspepsia is usually a prominent feature and in some cases it so completely dominates the clinical picture that Manson was originally led to describe this class of case as gastric sprue. The patient complains of a feeling of weight, oppression and gaseous distension after eating. Usually the abdomen swells out like a drum, unpleasant borborygmi course through the bowel and may be audible some distance from the patient. Occasionally this may be relieved by vomiting which may be sudden and not always accom-

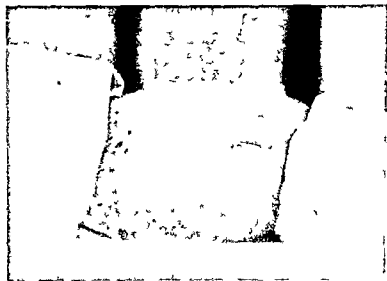


Fig. 64.—Showing meteorism and distension of the abdomen in chronic sprue with patchy pigmentation.

panied by feelings of nausea. Vomiting, however, as a constant feature is somewhat uncommon in sprue.

In some rare instances the rectum and vagina may be affected by a process of excoriation similar to that in the mouth. In elderly people a raw and painful condition of the anus is not uncommon. In 1934 the author saw a lady suffering from sprue in whom vaginitis was such a distressing feature that it had produced a state of kraurosis.

**Meteorism**—Meteorism may be extreme and in some advanced cases the distended coils of small intestine (especially of the ileum) may be seen mapped out on the surface of the abdomen where vermicular peristaltic waves may be visible. The abdomen is distended especially below the umbilicus and thus with obliteration of the normal outline of

the flanks, gives a barrel shaped appearance. In addition, the abdominal wall may become so wasted that it forms a very thin, almost diaphanous covering. The stomach, also, may be distended with gas and can be mapped out on the surface of the abdomen. Extreme dilatation of the stomach is usually associated with tetanic symptoms (Fig 64).

*Diarrhœa*—Diarrhœa associated with sprue is of two kinds, one chronic and habitual, the other more acute and, in the early stages, usually evanescent. In the chronic form diarrhœa is characterized by the passage of one or more copious, pale greyish, pasty, and fermenting stools, acid in reaction and of a peculiar sour smell. In the acute form it is more watery, but still pale and fermenting, containing masses of undigested food and usually large amounts of oil and fatty acids. Diarrhœa is usually attended with considerable relief, owing to passage of flatus and diminution of gastric distension. The typical sprue diarrhœa occurs in the early morning. The patient is frequently awakened at night or in the early morning by urgent desire to go to stool. Defæcation is accomplished with a sense of relief coupled with a feeling of exhaustion; tenesmus, or straining, is, however, present in a small proportion of cases during the acute and early stages of the disease. A frequent characteristic of sprue diarrhœa is the passage first of solidly formed motions, followed later by violent diarrhœa of an explosive character, in acute cases, scalding of the anal margin and of the perianal skin by the passage of so many acid motions may be very distressing. Very rarely, in a peculiar chronic form of the disease the stools have all the characteristics of the sprue stool, but diarrhœa is absent, in others, again, there may be chronic constipation.

In a series of 200 cases, the author and Willoughby have tabulated the main abdominal symptoms of sprue

#### 1 *Diarrhœa*

(a) Early morning	69 cases (34.5 per cent)
(b) Any time of day	116 " (58 " )
(c) Morning and evening	9 " (4.5 " )
(d) Night only	4 " (2 " )
(e) No diarrhœa throughout	1 case (0.5 " )
(f) Constipation and diarrhœa alternately	1 " (0.5 " )

#### 2 *Other Symptoms*

(a) Abdominal pain	79 cases (39.5 per cent)
(b) Flatulence	144 " (72 " )
(c) Meteorism	101 " (50.5 " )
(d) Vomiting	27 " (13.5 " )
(e) Anorexia	18 " (9 " )

*Shrinkage of the liver*—Diminution of the liver dullness was frequently noted by the older observers of sprue as being almost pathognomonic. In the series of cases already quoted, a diminution of liver dullness was noted in 56 per cent, and as the result of these observations it was established that the most marked shrinkage was present in the most advanced stage of the disease, usually associated with extreme anæmia.



Probably this liver shrinkage is but part of the wasting common to the disease

**Muscular cramps and tetany** — Cramps are a frequent concomitant of sprue and are present in some form or other in almost every well marked case especially in those with extreme wasting and anæmia. These cramps are noted usually in the muscles of the calves and thighs when the patient remains long in one position as in sleep. In the early stages when diarrhoea is present they may be so troublesome as to interfere with sleep passing off directly the diarrhoea ceases.

Tetany of the hands and feet has been noted in association with the predisposition to cramp in three instances in the author's series. The



Fig 65 — Tetany in sprue with low blood calcium content

hands assume the obstetric position in spasmodic contraction. Deep reflexes are increased occasionally Chvostek's sign can be elicited on striking on the angle of the jaw. Trousseau's sign (i.e. the production of tetany by compression of the brachial artery) is usually positive also. Tetanic contractions are associated with the low blood calcium due to disordered calcium regulation but pass off directly the patient is given large doses of calcium by the mouth or calcium gluconate (Sandoz) intravenously (Fig 65).

A young married woman was seen in April, 1934 on her return from India after a four years tour. In October 1933 typical sprue symptoms had commenced with diarrhoea and later sore tongue and mouth. No diagnosis of sprue had been made in India in spite of the great emaciation and typical symptoms which she presented. On entering hospital her weight was 91 lb. She complained of frequent attacks of cramp in her legs and arms with tetanic contractions. Trousseau's and Chvostek's signs were both positive.

The blood calcium was 7.5 mgm per 100 c.c. of serum, and the inorganic phosphorus 2.4 mgm per 100 c.c. of plasma. The accompanying anæmia was not extreme. The hæmoglobin was 82 per cent, red blood count 3,000,000, and colour index 1.2. The response to treatment by intravenous injections of calcium gluconate (Sandoz) 5 c.c. daily for ten days was satisfactory.

**Skin pigmentation**—A patchy pigmentation of the skin, mainly over face and abdomen, occurs frequently in association with the severe anæmia of sprue. Its origin has been discussed by Thaysen, who believes that it is due to some endogenous change and has no relation to adrenal deficiency or to blood destruction (Fig. 64).

In Ceylon the author noted pigmented patches, consisting of dark brown areas of irregular freckles on the forehead, temples and cheeks, in the abdomen (in two cases) and on the legs (one case). During the last twenty years, in practice in London, he has noted four other cases. In one lady of 47, from India, who was naturally the subject of leucoderma, the patchy pigmentation of the abdomen was so striking that it resembled the markings on a *Cypripedium* orchid.

**Larval sprue.**—As a rule, the characteristic condition of the tongue is associated with symptoms of gastric and intestinal trouble, but this association is by no means invariable. In 1912 the author described a number of cases of Europeans in Ceylon in whom the only manifestation of sprue was the peculiar condition of the tongue, and recently he has encountered other instances of this kind in Europeans treated for sprue in England. In these cases, an aphthous stomatitis of a particularly acute and distinctive type attacks the tongue and buccal mucous membrane, causing salivation, acute distress, and inability to swallow anything but the blandest fluids. The condition somewhat resembles acute syphilitic stomatitis, so the exact diagnosis may remain in doubt for some time. It may persist for a year or more before the advent of the characteristic gastro-intestinal symptoms. A typical case may be quoted—

A man of fifty-five, who had resided in India and China for many years, was seen in August, 1928. There was aphthous stomatitis with generalized glossitis, deep fissuring, and actual bleeding of the tongue. The process was so acute that the superficial epithelium of the tongue was removed, and he could neither eat nor swallow. Salivation was excessive. Finally œsophageal pain, with complete loss of taste was noted. Two months later he developed true sprue diarrhœa and secondary anæmia.

The recognition of the premonitory or 'larval' state in sprue brings this disease into line with pellagra.

**Special features of sprue in women**—In women amenorrhœa is a very prominent symptom, a feature which has not been adequately recognized. It does not seem to bear any close relationship to the development of sprue anæmia, but it has been found to be an early clinical sign. The ill effect of sprue upon pregnancy has long been

recognized it may actually lead to abortion. Usually the sprue symptoms become acute immediately after childbirth.

**Complete or typical sprue**—The history given by the majority of patients is somewhat as follows. He has been suffering for months—it may be for years—from irregularity of the bowels and symptoms of indigestion. The diarrhoea usually commences shortly after arrival in the tropics and for a long time it may be a simple biliousness and early morning diarrhoea. This continues without interfering very much with the general health. Later the mouth becomes tender, and aphthae appear for a day or two on the tip of the tongue and in the lips. If the patient is a smoker he will notice that pipe smoking becomes almost impossible. At the same time there is complete loss of the finer sense of taste. Gradually the stools lose their bilious appearance and become pale and frothy, the gaseous content may be such that they appear to bubble over. Dyspeptic symptoms especially meteorism and flatulence now become apparent particularly after meals. Anorexia coupled with loss of taste is usually complete. As time goes on the symptoms recur more and more frequently, especially after large meals, severe exercise, or even rapid changes in temperature. The general condition begins to deteriorate and the patient is assailed with languor and lassitude and is unable to get through the day's work. Emaciation becomes apparent especially in the region of the neck and his clothes hang from him as from a clothes peg. The condition progresses especially during the hot weather until a state of permanent invalidism is established. If the disease is allowed to progress unchecked he becomes more and more emaciated and the diarrhoea is constant during the whole of the day. The complexion alters, the skin being sometimes pigmented and there is usually complete anorexia. Any attempt to indulge in solid food is followed by increased discomfort which may be relieved by attacks of diarrhoea. At length the patient is confined to bed. The feet become oedematous and the skin dry, inelastic, scurfy, scaly, and of an earthy tint. Finally the patient dies from heart failure with choleraic diarrhoea, from marasmus, from extreme anaemia, or from some intercurrent disease.

**Incomplete sprue**—In some cases all the classical and cardinal signs and symptoms may not be present, as has already been pointed out, these incomplete cases fall into a definite category. In the author's series of two hundred cases they constituted 22 per cent. In this class the disease process appears to be confined to a limited part of the alimentary canal, thus a case may proceed to a fatal termination with diarrhoea and anaemia, the stool being typically liquid, copious, pale and frothy, yet mouth symptoms may be completely absent. In this condition there is as G. Thin remarks, usually tumidity in the epigastric region and a peculiar soft doughy feeling on pressure, this condition being sometimes very marked in contrast with the emaciation

of the limbs and thorax, but there is comparatively little pain or tenderness."

**Sprue without diarrhœa**—It sometimes happens that cases are met with in which the sore mouth, dyspepsia, and diarrhœa completely subside, but wasting continues, the stools remaining remarkably large—so large that the patient may declare that more is passed in the feces than can be accounted for by what he has eaten. In this condition the wasting becomes progressive and the patient gradually dies. On the other hand, the author has met with three patients who passed typical copious sprue motions, without any signs of emaciation or anæmia, and who otherwise appeared to be in good health.

**Mental disturbances**—The mental attitude in sprue is typical, and the whole character of a person may be changed in a curious manner. Those who were formerly reasonable and rational become cross and crotchety, as nurses, sisters, and attendants familiar with the "spruey" temperament know to their cost. Usually these idiosyncrasies manifest themselves especially in relation to diet. In some cases, particularly where there is considerable anæmia, there may be actual mental derangement. The usual psychological state is one of great depression and it is this which makes sprue such a difficult disease to treat. In this respect sprue is distinct from Addisonian anæmia, which it otherwise often resembles. As the mental outlook of sprue patients is very often profoundly influenced by the actions of their bowels, their return to good humour on the cessation of the diarrhœa and the more urgent symptoms of the disease is always to be regarded as an index of a return to a better state of health.

**Anæmia**—The anæmia of sprue has already been described from the laboratory aspect. From the clinical point of view there are two distinct forms. One is associated with the persistence of gastrointestinal symptoms, and appears to be dependent upon them, it usually becomes apparent when the disease has lasted for some considerable time. In all the cases of severe anæmia in the author's series diarrhœa has figured as a predominant symptom. The blood condition is of importance *pari passu* with the importance of the intestinal symptoms (Chart 11, p. 385). The second form is the anæmia which so closely resembles Addisonian anæmia, commencing *de novo* when all the main symptoms of the disease are in abeyance. It is this form that is subject to recurring hæmolytic crises.

**Pyrexia**—In the majority of cases the disease progresses, from the commencement even to a fatal termination in an apyrexial manner, cases of continued pyrexia due to the uncomplicated sprue process being apparently rare, but fever may occur in sprue as in other severe anæmias, the author has records of ten such cases. The temperature may reach 103° F. and be distinctly intermittent in character. It may be inferred that toxic absorption from the intestinal tract is an important

factor from the manner in which the temperature defervescens when the patient is placed on a suitable dietary

**Emaciation**—The emaciation of sprue which resembles that of chronic starvation exceeds that of almost any other disease, and may be so extreme that the patient loses almost half his body weight. Weight is, however, regained by means of suitable treatment in a remarkably short time. The cases here recorded were seen in 1913.

A planter of Ceylon, who had resided in the island for twenty six years developed symptoms of sprue, and lost 56 lb. in weight within four months. By treating himself in his own bungalow with milk, eggs, and fruit he eventually regained his normal weight of 178 lb., and when seen three years later was in good health.

In a second case, a man of fifty nine years of age, also a planter, had resided thirty nine years in Ceylon. He developed sprue in 1906, losing 70 lb. in weight in six months. After a period of treatment in England, he rapidly regained the weight he had lost, and when seen three years later was in apparently normal health. He then weighed 182 lb.

**Basal metabolism**—Very few observations have been made upon the basal metabolism in sprue. Such records as exist are by Kassirsky (1929), who studied seven cases of which five were normal, of the other two, in one there was a questionable increase (7.2 per cent. and 13.5 per cent.) and in the other case a pronounced increase, amounting to 28 per cent. E. H. Thaysen concludes that in sprue the basal metabolism has a tendency to increase but that this increase may subside as the patient improves under treatment.

**Blood-pressure**.—Usually, in anæmic cases, there are shortness of breath and signs of cardiac insufficiency such as œdema of the ankles, in these cases also, a basal systolic hæmic murmur may be heard over the heart. The blood pressure itself is usually much decreased. The author, with Willoughby, found that in sixty six cases the average systolic blood pressure was 20 mm. below normal, while the diastolic pressure was lowered by about 40 mm. The blood pressure is lower in the more advanced cases than in the early stages of the disease.

**Latency**—One of the most remarkable features of sprue is the latency which it may exhibit. A latent period of six to eight years' residence in Europe is quite common before the commencement of recognizable symptoms. The author has records of two cases, in one of which it was 25 years and the other 30. Prolonged remissions have also been noted, with relapses (in the author's experience) after an interval of apparent good health for 20 years or even longer.

#### COMPLICATIONS\* AND SEQUELÆ

**Intestinal atrophy consequent upon sprue**—In certain instances the symptoms of sprue disappear, but digestive and assimilative faculties are permanently impaired. Slight irregularity in the amount

\* It will be noted that many chronic complications of sprue have been found attributable to vitamin deficiencies.

of food, chill, fatigue, or an emotional disturbance brings about dyspepsia accompanied by flatulence and diarrhœa. Cases of this sort are prolonged for many years, in England they usually improve during the summer and deteriorate in the cold, damp weather of winter. Eventually the sufferers die of general atrophy or perhaps of some intercurrent disease.

**Œdema.**—A fleeting generalized œdema has been frequently observed in advanced and emaciated cases when assimilation and absorption have been restored, and the patient commences to put on weight. From the clinical aspect, the author regards this phenomenon as a nutritional œdema or water retention in the lax subcutaneous tissues. Œdema of the extremities is frequently observed in convalescent cases, but passes off when full activities are resumed.

General anasarca with ascites has also been recorded in cases of long standing. The author has seen two well marked examples in which the œdema was definitely of cardiac origin, and was associated with a moderate degree of arterio sclerosis. It cleared up after the exhibition of digitalis.

**Nerve lesions.**—Not infrequently sprue patients complain of paresthesias—usually a tingling or numbness of the fingers and toes—this being most frequently found in the cases with severe anæmia. It has always been considered that serious lesions of the nervous system are absent, this being a main distinguishing feature between sprue and Addisonian anæmia, in which peripheral neuritis and cord degeneration are essential concomitants (L. J. Wits). Nevertheless neuritic symptoms associated with chronic sprue have been noted in a retired official from Hong Kong, aged sixty five years, who had been under the author's care on and off for six years. Possibly this may denote a secondary B<sub>1</sub> deficiency.

During the whole of this period the sprue process had persisted in a subacute form and there had been severe macrocytic anæmia. In spite of the fact that the anæmia had always responded to intramuscular injections of liver (Campolon or Anahæmin) symptoms and signs of neuritis had become apparent. There was a persistent tingling sensation in both legs with some paresthesia, entire loss of ankle and knee jerks, and some difficulty on walking. It was this disability which caused him to be re admitted to hospital in March 1938. The response to Vitamin B<sub>1</sub> injections (Benerva 1 c.c.—25 mg crystalline Vitamin B<sub>1</sub> daily) was very satisfactory in clearing up these neuritic signs. After a series of twelve injections the knee and ankle jerks could again be elicited after three weeks. It should be added that on previous occasions he had been treated with large doses of liver without any ascertainable effect upon the reflexes.

The author has, moreover, encountered two examples of subacute combined degeneration of the cord accompanying sprue anæmia, in which it ran an acute and rapidly progressive course and proved to be terminal. Cord symptoms manifested themselves in ataxia of the limbs, ankle clonus, and positive Babinski signs, which did not yield to liver injections.

A man of fifty four, from Hong Kong, who was known to have suffered from sprue symptoms for twenty one years, was first seen in February, 1927, *in extremis*, with the most severe form of anaemia. The hæmoglobin percentage was estimated at 10, and the red blood corpuscles at less than 400,000 per cmm. Following blood transfusions he made a rapid recovery, and remained well until three years later, when he had a severe relapse for which further blood transfusions were required, recovery being much slower than on the first occasion. At the end of 1931 definite signs of cord disturbance were noted—tingling sensations in both legs, with sensory disturbances and stocking anaesthesia. Within a month he became definitely ataxic, with increased deep reflexes, ankle clonus, and positive Babinski sign. Marked muscular wasting was also present, with fibrillary twitchings of the muscles. With these signs of subacute combined degeneration, there was an increase of the anaemia. Death took place at the beginning of 1932.

A second patient, a man of fifty nine, of mixed Chinese and European descent, was born in Shanghai and had lived there all his life. When seen in April, 1932, he was from the clinical aspect, a typical case of sprue, with sore tongue, aphthous ulceration of mouth and lips, and large, pale, gaseous and copious stools. There was also extreme anaemia with typical blood changes. He complained of ataxia of both legs, with numbness and paraesthesia. After a course of treatment in hospital, with liver injections, etc., the anaemia and general condition improved, but the signs of subacute combined degeneration became more and more evident, and finally, previous to his return to Shanghai in September, 1932, he presented a typical clinical picture of that condition.

**Sprue secondary to dysentery and other abdominal diseases.**—Some authorities consider that sprue may be secondarily implanted on the bowel which has been previously affected by bacillary or amœbic dysentery. The statistical evidence in favour of this will be found on p. 338. Usually the patient gives a history that the motions, formerly characteristic of the original dysenteric attack, have gradually become changed in character. From being scanty, mucoid, and bloody, and accompanied by pain and tenesmus, they become diarrhoeic, pale and frothy, at the same time the mouth becomes sore. Hill diarrhoea is a frequent precursor of sprue and in many cases this somewhat trivial complaint merges into the more severe disease.

**Intercurrent illness affecting sprue patients.**—A list is given of the intercurrent diseases encountered in a series of two hundred cases.

Amœbic dysentery	2	Neurasthenia	2
Syphilis	9	Diabetes mellitus	2
Eczema	3	Pyorrhœa	3
Psoriasis	1	Acute appendicitis	5
Pneumonia	2	Malaria	4
Alcoholism (acute)	1	Duodenal ulcer	1
<i>B. coli</i> infection of the urinary tract	10	Renal calculus	1
Peripheral neuritis	1	Septicæmia	1
Ancylostomiasis	1	Giardiasis	1
Rectal polypus	1	Hæmorrhoids	2
		Scurvy	2

tertiary syphilis is frequently combined with sprue and exerts an influence on the course of that disease so that it must be regarded as a primary factor in determining treatment. Syphilis may not be made manifest by physical signs but is detected by the routine performance of the Wassermann test. Occasionally tertiary syphilitic lesions of the tongue are seen in sprue and it is important that the manifestations of the two diseases should not be confused (Fig 63 and Plate XII). The author once observed manifestations of sprue and syphilis in the tongue at the same time.

Bad teeth and pyorrhœa must necessarily be attended to only after the subsidence of the more acute symptoms of sprue. Great care must be exercised in advocating a time in which dental interference may be undertaken. The author has seen too rapid and vigorous extraction provoke a serious relapse. It is a mistake to suppose that oral sepsis has anything to do with the genesis of sprue.

Co-existing infections are apt to complicate sprue e.g. syphilis. *Bacillus coli* infections of the urinary tract probably due to general debility, malaria especially the benign tertian form which may provoke relapses, amœbic dysentery, lung complications such as lobar pneumonia and acute appendicitis quite a common complication. The author has also seen a combination of diabetes and sprue, thus constitutes an almost insuperable problem mainly because the dietary that suits sprue aggravates diabetes and *vice versa* insulin treatment has proved unsatisfactory. There are certain cases of sprue which appear to be complicated by a mild degree of pancreatitis and in these the exhibition of liquor pancreaticus and pancreatic extracts appear to be followed by good results.

The effects of intercurrent disease upon the progress of sprue constitutes a curious and it may be a difficult problem. The author has seen two cases which recovered completely after passing through a severe attack of pneumonia and two others which were greatly benefited by an attack of appendicitis and subsequent appendicectomy. In July 1931 he treated a fairly severe case of sprue in a tea planter from India aged thirty eight. He subsequently suffered from relapses and in May 1939 contracted severe cholera from which he nearly died. Since he recovered he has had no more symptoms of sprue.

**Skin lesions**—Sprue cases when responding satisfactorily to treatment are specially liable to a form of papular eczema. The author had experience of many such cases especially in elderly patients and they yield to applications of ichthyol and glycerin. This is a particularly annoying and intractable complication of convalescence.

**Scurbic purpura**—There is a distinct tendency for atrophic sprue cases to develop petechial hæmorrhages especially of the hands (Fig 66). Any little lesion such as a bruise may be followed by considerable hæmorrhage. This is specially likely in those cases which have been continuously fed on an artificial milk dietary. The author has had experience of two cases in which a purpuric rash appearing on the legs



and arms, exhibited the typical distribution of a scorbutic rash (Fig 67) In both instances it disappeared immediately a diet of orange juice was instituted It is probable therefore, that the hæmorrhagic tendency in sprue is scorbutic in nature and denotes a vitamin C deficiency This feature was first noted by H Werner (1914)

Very often in advanced cases with severe anæmia, numerous bluish grey subcutaneous patches are noted, especially on the legs, and the patient is liable to bruising after the least injury These patches were specially noticeable in a female patient from India aged forty four, who was treated in 1931 They rapidly disappeared on an antiscorbutic dietary reinforced with adequate doses of calcium lactate A hæmorrhagic tendency occasionally accompanies idiopathic steatorrhœa which has recently been ascribed to vitamin K deficiency (see p 412)



Fig 66—Petechial hæmorrhages on the dorsum of the hand in chronic sprue with extreme atrophy

**Scurvy as a complication of sprue**—A ship's engineer aged thirty, contracted sprue in Bombay in August, 1925, and lost 64 lb in weight He was fed on a tinned milk dietary on the homeward voyage Six days after admission to hospital he showed definite signs of scurvy including bleeding of the gums and a purpuric rash on the legs and thighs The addition of an



Fig 67—Scurvy rash in sprue, showing distribution of petechiæ round hair follicles (vitamin C deficiency)

orange a day to the diet caused such an improvement in his condition that he was discharged after nine weeks in hospital, having gained 28 lb

A retired Colonel of the Indian Army, sixty five years of age, and previously treated by the author in 1924 for a primary attack of sprue had a relapse in July, 1932. He lost 42 lb in weight and presented the familiar symptoms. In spite of the generally accepted dietetic measures he lost ground and his condition became serious when, in September, he developed scorbutic purpura—a discrete scorbutic rash on both legs—with spongy, bleeding gums and deafness. He was then placed on a fruit dietary and immediately began to improve and eventually regained his normal weight of 13 stone 6 lb

**Secondary pellagra in sprue yielding to nicotinic acid**—Typical secondary pellagra with skin manifestations in sprue has now been observed in one of the author's recent cases (1938). This was in a man, aged sixty, from Hong Kong, who had suffered from sprue symptoms for eighteen years during which time he had been dieting himself more or less strictly on a meat milk dietary. Two and a half years after his return to England he developed skin rashes and pigmentation of the scalp, face, neck, hands elbows knees and scrotum together with a red raw pellagra tongue deep fissures at the angles of the mouth (*see* p 363), and psychological disturbances. At the same time typical sprue megalocytic anæmia was present together with diarrhœic fatty stools and excess of fatty acids (57 per cent). The response to nicotinic acid (150 mgm per diem for ten days plus 50 mgm per diem for six weeks) was striking. The sprue symptoms disappeared and the pellagrous rash faded. He increased 18 lb in weight while maintaining his former dietetic restrictions. The history of this case clearly demonstrates that in chronic sprue Vitamin B<sub>3</sub> (the PP factor of pellagra) may be concerned just as in the case of Vitamin B<sub>1</sub> and Vitamin C (pp 371 and 374) and lends weight to the contention that sprue and pellagra probably are allied diseases.

### DIAGNOSIS

The diagnosis of sprue is mainly effected on clinical grounds—the history of the case, the appearance of the tongue and mouth and the character of the stools being sufficient to render it easy to those familiar with the disease. But when sprue commences in England in a person who has previously resided in the tropics it is likely to be mistaken for other intra abdominal conditions.

### DIFFERENTIAL DIAGNOSIS

**Addisonian pernicious anæmia**—The differential diagnosis from true Addisonian, or pernicious, anæmia is not always an easy matter. In this disease there is achylia gastrica, whereas in sprue there is usually hypochlorhydria with response to histamine (*See* p 359). Sprue exhibits a typical megalocytic anæmia yet normoblasts are rare and high Van den Bergh serum bilirubin readings—which are the rule in true pernicious anæmia—are exceptional. The stools of pernicious

anæmia are apparently normal. There is rarely the degree of emaciation which is seen in sprue—in fact, the body is generally well nourished, and the heart and other organs are not wasted to the same degree. The tongue in Addisonian anæmia may be normal or may have undergone inflammatory changes, whereas in sprue the process is more localized (Plate XII, 3), the glossitis in both cases is probably similar.

*The syphilitic tongue* is characteristic, being distinguished by leucoplakic patches, often deeply fissured and irregular in shape. Often small sinuous ulcers or excoriations may be observed, and the submaxillary lymphatic glands are usually enlarged (Plate XII, 4). The tongue is not particularly painful, though the finer senses of taste are usually obliterated. The sprue process appears to attack the fungiform papillæ, especially at the tip, where they become red, swollen, and extremely painful. It is localized and is associated with great sensitiveness, and usually with aberrations in taste. Small aphthous ulcers are commonly seen on the tongue or buccal mucosa, and these are sufficiently characteristic to aid diagnosis.

Glossitis is seen in pellagra, B<sub>2</sub> avitaminosis and idiopathic stenterorrhœa (See p. 410). In all forms of anæmia, atrophy of the papillæ may be observed, and is noticeable in the terminal stages of ancylostomiasis.

*Rough and fissured tongue*—An extremely ragged and rough tongue with accentuated clefts or fissures is commonly encountered in native races. Both filiform and fungiform papillæ appear to be hypertrophied. The author has frequently encountered this form in Europeans, in whom it appears to be hereditary and a family characteristic usually associated with hyperchloremia (Plate XII, 6).

† *Geographical tongue*—(Plate XII, 5) is occasionally encountered, and apparently has no relationship to gastro intestinal disease. Here the process consists of desquamation of the superficial epithelium, which, spreading laterally, produces an odd appearance which has been compared to a map of the world. Geographical tongue is usually seen in hypersensitive children, and may cause pain and irritation.

*Tongue of larval pellagra*—During his researches in Ceylon in 1912-13 the author described a red raw excoriated tongue over the greater part of which destruction of the superficial epithelium takes place (Plate XII, 2). It was found among prisoners and the inmates of institutions in which salted fish formed the principal article of diet. With the raw and red tongue there is an excoriated and eczematous condition of the angles of the mouth (angular stomatitis) and a leucoplakic condition of the lips (perlèche). At that time, the author was inclined to believe that it was a manifestation of pellagra. In 1933 L. Nicholls made further observations on this tongue and, finding that it was associated with mild neuritis and definite eye symptoms, suggested that it was due to avitaminosis B<sub>2</sub>. Clinical response to nicotinic acid (T. D. Spies) has conclusively demonstrated the correctness of this view.

The case of a married woman, aged sixty-two, was (1938) investigated by the author, to whom she had been referred as a case of sprue contracted in South Africa. She had been ill for five years with constant diarrhoea and stomatitis,

in consequence of which she had been subsisting on a low grade dietary. The tongue was red and raw with destruction of all the papillæ, an associated 'angular stomatitis' and perleche of the lower lip. There was also severe non fatty diarrhœa and a mild grade microcytic anæmia with hyperchlorhydria. The case was regarded as one of B<sub>2</sub> avitaminosis. Response to nicotinic acid, 150 milligrammes daily, was immediate. Within twenty four hours she noticed the absence of pain in the tongue for the first time, and within five days the papillæ became once more apparent, the diarrhœa ceased entirely, and the depression and lethargy from which she had suffered disappeared. She regained her health and put on 7 lb. in weight within two weeks.

J. V. Landor and R. A. Pallister confirmed the observations of Nicholls in Ceylon and of G. D. Fitzgerald in Assam. They described what is undoubtedly the same disease in Malaya, particularly in institutions. The main lesions are eczema of the scrotum, and of the angles of the mouth and superficial glossitis, and in the later stages the symptoms are those of combined degeneration of the cord and impaired vision. They, also, consider that it is due to avitaminosis B<sub>2</sub>, a theory receiving considerable support from the fact that a similar glossitis occurs in pellagra (*see* p. 331) and from the fact that like pellagra it can be prevented by a well balanced diet.

In 1918 H. H. Scott, in Jamaica described a 'central neuritis' as tending to occur in epidemic form among labourers on sugar estates, in whom a similar condition of the mouth and tongue was encountered. In 1928 E. J. Wright discovered the same disease in Sierra Leone among a poor class of native, and in 1934 Fitzgerald Moore found it in Nigeria especially in school girls in whom it is associated with retrobulbar neuritis leading to optic atrophy, in males it was associated with a scrotal rash.

*Glossitis associated with dyspepsia*—This list does not exhaust the tongue changes with which sprue may be confused. In grave degrees of dyspepsia associated with gastric hyperacidity, a transient glossitis is often seen. In 1936, the author encountered such a case in a woman who was thought to be suffering from sprue on account of diarrhœa with pasty stools, together with an excoriated condition of the tongue. A fractional test meal revealed an exceptional degree of hyperacidity, a prolonged acid curve with no marked response to histamine—up to 0.474 per cent of free hydrochloric acid. A barium meal showed gastrospasm which disappeared after treatment with alkalis and belladonna.

*Glossitis of diabetes*, which is confined to the tip of the tongue is also sometimes met.

*Cœliac disease*—From cœliac disease (intestinal infantilism or the Gee Herter syndrome) the problem of differentiation is by no means easy. Cœliac disease occurs as a rule, in children and is frequently seen in those who have been reared in the tropics. As has been pointed out by H. Miller, the ætiology is probably different from that of sprue and depends upon an inherited inability to absorb fat (*see* p. 406). Cœliac disease persisting to adult life is now known as idiopathic steatorrhœa.

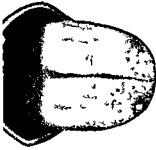
**Chronic pancreatogenous fatty diarrhœa**—The differentiation of sprue from this disease is by no means always easy because in both there are steatorrhœa, emaciation, meteorism and diminution of the liver dullness and in both there may be anæmia and occasionally tetany.

In chronic pancreatitis stomatitis is absent and there is usually no anæmia. The feces of pancreatogenous fatty diarrhœa are usually composed of an oily yellow substance which consists of neutral fat (see p. 415) and as a rule the amount is greater than in sprue, the daily average output sometimes being as high as 65 grammes. Thaysen attaches great importance in the differential diagnosis to the nitrogen elimination which is increased in pancreatitis but seldom in sprue. The enzyme content of the duodenal juice is normal in sprue, lowered in chronic pancreatitis.

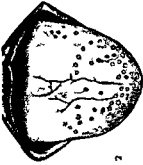
**Tropical macrocytic anæmia\*** (tropical megalocytic anæmia, tropical anæmia of pregnancy) is a severe megalocytic hyperchromic anæmia of nutritional origin in which the blood picture resembles that of sprue. It especially affects pregnant women in the tropics and responds specifically to the administration of marmite and liver extract with a reticulocyte response and rapid blood regeneration. The Price-Jones curve resembles that of Addisonian anæmia but the serum bilirubin is not increased. A similar condition has been reported in males among the native population of India, Malaya, China, West Africa and also Macedonia, wherever the dietary is unbalanced and unsatisfactory. The age incidence is generally between fifteen and thirty years of age. This anæmia also differs from Addisonian anæmia by the presence of free hydrochloric acid in the gastric juice. Marmite cures this condition but it has recently been shown that vitamins B<sub>1</sub>, B<sub>2</sub> and B<sub>6</sub> are not responsible for this result, the curative factor probably arising from a protein breakdown during autolysis.

**Pellagra**—The differential diagnosis between sprue and pellagra may be difficult. In those countries where the two diseases are found side by side, for instance in the West Indies and in the southern United States, the difficulties may be considerable, and some authors—notably F. J. Wood—have considered them identical. There very frequently occurs in pellagra a sprue like diarrhœa but whereas in sprue the stools are excessively large in pellagra this is not the case. Further in sprue there is an increased fat content of the feces and in pellagra the fat absorption is normal or slightly lowered. In acute pellagra a generalized stomatitis occurs with eczematous ulceration (cheilosis) at the angles of the mouth which is usually associated with gastrointestinal symptoms (Plate VIII, 2). Other differences are that pellagra affects the nervous system leading to severe psychoses and that it is not associated with any severe degree of anæmia. There is in addition the characteristic pellagra rash wherein pigmentation

\* It has been suggested that nutritional megalocytic anæmia would be a more appropriate term.



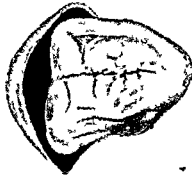
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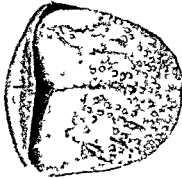
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*1 H. M. van der BEEK*

1 Tongue of acute sprue showing characteristic pythous lesion 2 Tongue of B2 vitaminosis and pellagra to demonstrate fissures and rhagades at angles of mouth (painted in Ceylon 1912) 3, Tongue of pernicious anemia the glossitic anemia of Hunter Note general atrophy associated with inflammation 4 Tongue of tertiary syphilis with leukoplakia 5, Geographic tongue in a girl of twelve 6 Rough fissured tongue with hypertrichia

persists during the quiescent periods, sufficient to distinguish it from sprue (see Table XIV, p 382)

*Addison's disease*—The symptoms of sprue may be interpreted as signs of adrenal insufficiency, and the presentation for that of Addison's disease. Fatty diarrhoea, however, which is the cardinal sign of sprue, is not usually encountered in Addison's disease, nor is the characteristic anaemia. The persistent low blood pressure of the latter disease (systolic under 100 mm.) and its response to injections of adrenalin, also aids in differential diagnosis.

**Gastro-jejuno-colic fistula** may cause fatty diarrhoea associated with glossitis, emaciation and anaemia. S. Strauss (1921), De Rivas (1930), N. H. Farley and T. P. Kilner have called attention to the possibility that such a condition may be mistaken for sprue. The last named have described four cases in which some of the symptoms observed in sprue were present—the fatty diarrhoea, emaciation and glossitis, associated with hyperchromic anaemia, in three of the patients gastro-enterostomy had previously been performed (see p 340).

**Disease of mesenteric glands.**—For some time it has been recognized that the clinical syndrome of mesenteric lymphatic obstruction whether due to tuberculosis or to lymphadenomatous deposits closely resembles that of sprue.

W. H. Allchin (1907) described a clinical syndrome resembling sprue in *tabes mesenterica*. In children, he says besides the fatty and milky stools, "the tongue is red irritable, or denuded of epithelium. Massive tuberculosis of the mesenteric glands is seen mostly in children, and appears to be especially common in Scotland. It is usually a primary mesenteric infection but may be associated with tubercular peritonitis. The symptoms consist of wasting diarrhoea with the passage of light coloured fatty faeces, a distended, doughy and hyper resonant abdomen, and, in some cases, a moderate pyrexia and a secondary anaemia. The enlarged mesenteric glands may be difficult to palpate, owing to abdominal distension until the disease is well advanced, so that this method cannot be relied upon. *Tabes mesenterica* with these spruelike symptoms may not be very difficult to recognize in children, but it is otherwise with adults. For instance—

In January, 1931, the author had under his care a retired Indian Army officer, who was referred to him as suffering from sprue as the result of his twenty years service in India. He died, after a prolonged and sprue like illness, in November, 1932. The case was a very puzzling one. The preliminary symptoms which began two years before admission to hospital, resembled those of sprue, and he had suffered during his service in India from amoebic dysentery and hill diarrhoea, both of which are common precursors of sprue. There had also been a rapid loss of weight (28 lb.) for two years. On looking back on the history it appears that suspicion of tuberculosis should have been excited by the fact that an enlarged, presumably tuberculous, gland in his neck had been excised when he was twenty three. Moreover, a radiograph of the abdomen revealed a large calcified retro caecal gland, and definite fibrosis (healed T. B.) at the apex of the right lung.

First impressions suggested sprue with a past history of tuberculosis. This supposition was supported by the abdominal meteorism, the pale, bulky stools (14 to 16 oz.) containing fatty acid crystals, and the definite excoriation of the buccal mucosa, with sprue-like inflammation of the tip of the tongue. Against the diagnosis of sprue were the facts that the amount of fat in the stools was relatively small (26.7 per cent.) and that the anemia (R B C 4,000,000, hæmoglobin 70 per cent.) was of the secondary type, with a colour index of 0.8. The blood calcium was, however, low (9.6) and blood cholesterol 119 mgm. per cent.

In August, 1931, the retrocecal glands had become palpable and enlarged. Palpable glands appeared in the right groin. A chronic inflamed appendix was removed, and from that time the course was progressively downhill, with great wasting and diarrhoea. At autopsy, an enlarged calcified gland,  $1\frac{1}{2}$  in in diameter, was discovered, posterior to the cæcum, while all the mesenteric glands were enlarged and showed, on section, the histological picture of chronic tuberculosis.

C. W. Ross (1936), in three cases of *tuberculosis mesenterica* in children, found oral sugar curves of the flat type, such as occur in sprue and celiac disease, and concluded that defective absorption of carbohydrates was responsible.

**Malignant disease**—Lymphosarcoma or lymphadenoma of the *mesenteric glands* may give rise to a clinical picture somewhat resembling that of sprue. So may also lymphosarcomatous infiltration of the lower end of the ileum, as in the case described by J. G. Willmore (p. 381). However, in lymphadenoma, palpable tumours or masses sooner or later become apparent in the mesentery, and the stools, though light coloured and fatty, do not contain the same constant high fat-content as in sprue.

In April, 1928, a young woman, twenty-six years of age, was admitted to hospital with a tentative diagnosis of sprue. She was born in Siam, had lived there until she was fourteen years old, and since then had lived in England. Six years after leaving the tropics, she suffered from chronic diarrhoea with some wasting (14 lbs.) but at first it had been easily controlled by a suitable dietary. The stools numbered between four and seven a day, and were pale, copious, and frothy. The fat content was high (63 per cent. of dried faeces, combined fatty acids, 30.5 per cent.). The abdominal distension was great, and there appeared to be sacculations of the transverse colon. The tip of the tongue was definitely red and sore, with prominent fungiform papillae. There was a short irregular pyrexia. Certain features of the case militated against the diagnosis of sprue. There were, for instance, a persisting and progressive leucocytosis of from 14,000 to 24,000 (polymorphs, 70 per cent., lymphocytes, 25 per cent.), and a secondary type of anaemia. The faeces were searched frequently for tubercle bacilli in vain. In July, 1928, she began to complain of pain in the centre of the abdomen and referred pain in the back, and in definite masses became palpable in the mesentery. An exploratory laparotomy in July revealed some cloudy free fluid in the abdominal cavity, nodular masses occupying the whole of the mesentery, and similar masses in the cæcal region. Microscopic sections of the growth revealed the typical picture of acute lymphadenoma.



N H Fairley and F P Mackie (1937) have described a series of four cases of lymphosarcoma in which the clinical syndrome resembled sprue tongue symptoms abdominal distension visible peristalsis and steatorrhœa being present. Glucose curves in these cases were similar to those of sprue and were due to defective absorption from the intestinal tract a factor responsible for the steatorrhœa.

Malignant disease of the *small intestine* may also produce a clinical picture of sprue. In 1924 J G Willmore described a patient from whom a lymphosarcomatous growth infiltrating the ileum had been removed. The faeces in this case were typically sprue like and on analysis contained 53.7 per cent of fat of which 20.59 per cent was neutral fat and 29.11 per cent fatty acid. Signs of intestinal obstruction becoming urgent an emergency operation was performed which revealed a malignant stricture at the junction of the upper two thirds with the lower third of the small intestine with enlarged mesenteric glands. Resection with lateral anastomosis was followed by uninterrupted recovery. After operation the faeces became normal in size and colour and contained 25.93 per cent of fat. The patient died two years afterwards from a recurrence.

**Syphilis** —Differentiation from syphilis affecting the mouth or the bowel is best decided by means of the Wassermann (or Kahn) test but it must of course be appreciated that sprue and syphilis may co exist in the same patient. In the author's series of 200 cases there was associated syphilitic infection in nine.

**Radiographic appearances** —The radiographic appearances of the bowel in sprue have been investigated by Pillai and Murthi. In acute cases there is no indication of the loss of tone or motility in the stomach or intestine. The stomach empties in two hours after the barium meal and the intestine in six to eight hours. In the subacute condition there is loss of tone and diminution in the peristaltic action. In chronic and atrophic cases the terminal coils of the ileum are greatly dilated the lumen of the bowel is distended the outline of the transverse colon is smoother than normal and marked haustration is absent. These findings agree with those ascertained by routine radiography in the Hospital for Tropical Diseases London.

D K Miller and W H Barker (1937) have shown that the most significant abnormalities are distortion of the mucosal pattern and a variation of the calibre of the intestinal loops. Striking changes were observed in the jejunum the normal delicate feathery pattern being replaced by one of coarser texture. The loops of the small intestine were dilated especially in severe cases. Successful treatment resulted in disappearance of radiographic abnormalities. This has been confirmed in the main by M Feldman (1938). T T Mackie and M A Mills (1940) also describe as characteristic changes commonly seen in the duodenum and jejunum where the mucosal pattern is coarser than normal with striking variations in contour and size of the lumen. In

TABLE XIV

	FERNICIOUS AFRICA	TROPICAL ASIA	INDOPACIFIC OCEANIC	PELLAGRA (Larval cases common)
	40-60 years	20-60 years*	20-60 years	20-50, but may commence in infancy
Etiology	Apparently absent or rare in tropical natives. Mostly in well fed Northern Europeans	Particular tropical distribution—(Central Africa exclude it) Mostly in Europeans and well fed people	Mostly Northern Hemisphere	Mostly tropics and subtropics in all-nourished people.
	Intrinsic factor absent does not return on treatment Predisposed by acrid gastrica Atrophic gastritis	Intrinsic factor absent, returns on treatment. Hypochlorhydria. (Achlorhydria gastrica rare) Atrophic gastritis Previous intestinal disease predisposing factor	Allied to, or sequel of "cervical diseases" in infancy Developmental defect of fat absorption Achlorhydria rare.	Deficiency disease of dietetic origin Deficiency of PP factor (vitamin B <sub>1</sub> ) Frequently secondary to chronic intestinal diseases, such as intestinal tuberculosis, bacillary dysentery and sprue Achlorhydria in 40 per cent of cases Achlorhydria rare
	Onset from hours Glossitis common, dysphagia rare Wasting slight Spontaneous remissions distinct feature Diarrhoea frequent Bilious stools Pyrexial like polymenitis Clashes in central nervous system common (subacute combined degeneration) No bone changes.	Onset insidious Glossitis common Wasting extreme Remissions distinct feature Steatorrhea Fatty acid stools Whole alimentary tract involved, especially small intestine Colon occasional Changes in central nervous system very rare Osteoporosis not observed	Onset insidious Glossitis and dysphagia common Wasting extreme Diarrhoea frequent, steatorrhea. 50 per cent fat mainly split—soaps. Megacolon common Changes in central nervous system uncertain Tetany and cramps frequent Pains in bones—kyphoscoliosis Genit valgum osteoporosis. Fractures Clubbing of fingers, lens opacities	Onset insidious Affected by sun's rays, spring recurrences Glossitis and dysphagia common Wasting no feature Prodromal symptoms common Diarrhoea frequent, + dyspepsia. Stools, bilious, may be fatty—usually suppurative intestinal infection Eruption — dermatitis — hands, face, arms scroto — always symmetrical

	PERNICIOUS ANEMIA	THROMBOTIC SPRUE	IDIOPATHIC STEATORRŒHA	PILLAGRA (Larval cases common)
—cont—			Infantilism in severe grades Absorption affected by fat, meta- bolism Tendency to hemorrhages	Changes in central nervous system resemble subacute combined de- generation Mental symptoms irritability, ex- citability, melancholia No osteoporosis, but fragility of bones
ogy	Megalocytic anemia and leuco- penia. Megaloblastic hyperplasia of bone marrow Bilirubinemia Blood glucose curve normal Blood calcium normal	Megalocytic anemia and leuko- penia. Bilirubinemia occasional Flat blood glucose curve Hypocalcemia Tetany and cramp occasionally Bone marrow atrophic	Megalocytic, hypochromic anemia and leucopenia, or single hypo- chromic anemia Bilirubinemia absent Flat blood glucose curve Hypocalcemia extreme	Megalocytic, hypochromic anemia and moderate leucopenia in a proportion of cases. Bilirubinemia absent Blood glucose curve normal Blood calcium normal Urine porphyrins in excess
ment	Responds to liver fraction Campeleon or Analeverum and to some extent to vitamin B <sub>12</sub>	Responds to liver fraction Campeleon or Analeverum intramus- cularly in large doses + vita- min B <sub>12</sub> (Nicotinic acid)	Responds to some extent to liver in large amounts vitamin B <sub>12</sub> and vitamin D	Responds to vitamin B <sub>12</sub> —Nicotinic acid and riboflavin
1933	Relapses inevitable unless recer- voir dosage of liver extract is maintained	Spontaneous recovery frequently observed May commence <i>de novo</i> in England 25-30 years after return from the tropics.	Spontaneous remissions of short duration	Spontaneous remissions tend to occur in untreated cases

\* In the author's series the average age of onset is 45 years.

the small intestine motor activity is disturbed and there is segmental distribution of the barium in dilated coils (see also p 413) These abnormal appearances can be reasonably explained by physiological changes in the small intestine

**Sigmoidoscopic appearance of the bowel in sprue**—The author has studied the appearance of the bowel in sprue in the acute as well as in the chronic stage of the disease In the former the mucous membrane is injected and has a bright, rosy pink colour, with absence of mucus and loss of the lustre peculiar to a healthy mucosa In the chronic stage the bowel wall is attenuated and the mucous membrane is lax diaphanous, of a pale grey colour with lack lustre and atrophic appearance Sigmoidoscopy may be of considerable assistance in the diagnosis in doubtful cases The author has been able to employ it on several occasions in those subacute cases in which the cardinal symptoms are either suppressed or evanescent

The sprue process commonly extends into the large intestine, indeed it may affect the mucous membrane of the whole tract The changes seen in the upper rectum may then be taken as an indication of the pathological appearances throughout the intestinal tract Often, too the characteristic pale, wax like, semi-solid faeces may be observed pouring down the rectal canal from the sigmoid This may be pathognomonic

#### TREATMENT

The treatment of sprue is one upon which many views are held and in this work consideration will be given to the opinion of others For the most part it consists of bodily rest and careful dieting in order to procure assimilation If treatment is started sufficiently early and persisted in the result is usually successful but if it is commenced later when intestinal atrophy has progressed too far the disease is almost sure to be fatal It is certain that diet is the sheet anchor in the treatment of sprue and specific treatment is auxiliary It is necessary to point out however that there is a distinct individual and psychological aspect of the case which must be taken into account in the dietetic treatment of sprue idiosyncrasy plays an important part the majority of sprue patients being of the intelligent impressionable and introspective type Some thrive on one dietary others on a somewhat different one There are those for instance who are partial to and can digest milk products while in others the exact opposite obtains

At the outset the physician must endeavour to get on good terms with his patient co operation being essential for success since treatment may be long and tedious Careful and sympathetic nursing is fully as important as the medicinal treatment, and the patient should look forward to his meals—not resent his dietetic regimen if he does it will do him no good

Every case of sprue must be investigated from all points of view before active treatment is undertaken, and any associated conditions,

such as uterine discharges, syphilis, scurvy, dysentery, or helminthic infection, must be dealt with as far as possible. The weight of the faeces should be determined daily by weighing pan and contents and subtracting from the total the known weight of the former. The average weight of normal faeces is from six to eight ounces per diem, in sprue it may be twice or three times this amount. By making a chart of the average daily excretion, an estimate may be formed of the progress of the patient. The problem of diet in sprue is one of restoring the balance of absorption, in which connexion the reader is referred to Charts 11-13.

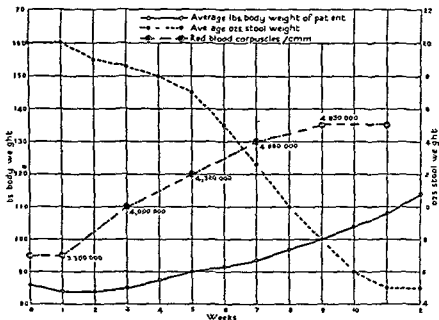


Chart 11 — Composite graph of ten cases of sprue to show the relative increase in body-weight together with the increase in red blood-corpuscles per cubic millimetre and with decrease in average weight of the stool

Although there are many opinions as to what comprises the most suitable dietary, it is agreed that two principal food constituents—fats and starches—cannot be completely digested or assimilated. The introduction into the diet of as much easily assimilable protein as the patient is capable of absorbing is therefore indicated.

So many different lines of treatment have been advocated that it becomes a matter of difficulty to decide which is the best. There have been fashions in the treatment of sprue as there have been in that of many other long continued and chronic diseases. The modern idea underlying treatment is to place it as far as possible upon a scientific basis to lay down a scientific diet and adhere to it as much as possible.

**Mixed diet**—Most cases of average severity, and those in which anemia is not a marked feature, thrive on a diet combining blandness with variety and avoiding those elements, viz fats and starches, of which the patient is intolerant. As much easily assimilable and non-irritating protein as the patient is capable of absorbing should be given. The aim is to restore the balance of absorption (Chart 11) and it is with this purpose and from the construction of graphs of this

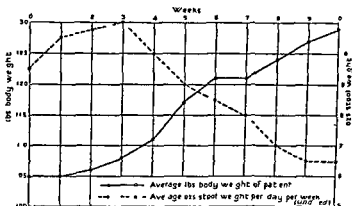


Chart 12—Graph illustrating that decrease in amount and weight of stool in sprue runs parallel to increase in body-weight (Average of ten cases.)

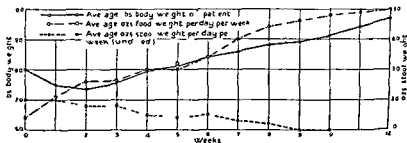


Chart 13—Graph illustrating the intake of solid matter in the food in sprue and its effect upon the weight of the stools.

nature that the author has designed his treatment of average cases. Observations on a number of cases have shown that on a mixed milk and protein diet, with the patient in bed there is a loss of weight amounting to 5 lb during the first two weeks of treatment possibly due to elimination of tissue fluids. When once equilibrium has been established, a gradual increase of body weight occurs. It can be shown, furthermore, that any alteration in the amount and weight of the stool passed by the patient on this dietary is in inverse ratio to his change in

body weight and the smaller the average size of stool the greater the increase in weight (Charts 12-18)

Remarkable increases in body weight have been recorded by the author e.g. one of 28 lb. in twenty one days and another 37 lb. within forty days. In his series gain in weight was obtained in 73 per cent. The average increase per patient was  $9\frac{1}{2}$  lb. and the average increase per week  $1\frac{1}{2}$  lb. Usually it is rapid for three or four weeks but after that becomes more gradual (Figs 68-69)



Fig. 68—Appearance of patient 24102 before treatment. Weight 88 lb.



Fig. 69—Appearance of same patient 5126 after course of dietetic treatment.

Another point to note is the average weight of the stool in those cases which are progressing favourably on a given dietary. As the intake of solid food and its assimilation progresses this increases up to a certain point after which a gradual decrease is noted. Therefore from the clinician's point of view the size and weight of the stool should not be taken as an indication for restricting the patient's dietary especially when associated with progressive increase of the body weight.

It is not necessary to give milk or substitutes alone for more than one week. Egg, sago and liver soup may then be added.

## DIETS FOR ACUTE SPRUE

## Diet No 1. First Week

(Total calorie value, about 1,000 calories)

Three pints (60 oz.) of cow's milk or Benger's food, in 5 oz. feeds at two hour intervals, toast, "pulled bread", "Heudebert" rusks, or digestive biscuits with a scrape of butter

## Diet No 2 Second Week

(Total calorie value, about 1,900 calories)

Three pints (60 oz.) of cow's milk or Benger's food as in No 1; rusks; toast, sago, 6 oz., liver soup, 12 oz., in two feeds of 6 oz. each. One lightly boiled egg; weak tea, or sprue tea (i.e. tea infused with milk), 8 oz.

## Diet No 3 Third Week Onwards

(Total calorie value, about 3,900 calories)

*Breakfast*—Porridge, or gruel, 1 egg, toast and weak tea

*11 a.m.*— 10 oz. of milk, Sprulac or Benger's food

*Lunch*— Liver soup, 12 oz., minced chicken, 6 oz., spinach (or cauliflower), 3 oz., sago (or semolina), 6 oz., baked apple or mashed banana, 6 oz.

*Tea*— Toast, tea, madeira cake, sponge cake, digestive biscuits (McVitie & Price), 3 oz.

*Dinner*— Brain or sweetbread, 4 oz., calves foot jelly, 3 oz., arrowroot, sago, or tapioca, 8 oz.

Diet No 1 is adjusted to a low calorie value, and while taking it, the patient must be kept in bed and carefully nursed. Diet No 2 is of a higher calorie value, while on this the patient may be allowed to sit up and use the lavatory. During the third, convalescent, diet, he may be allowed up in the afternoon.

It has been the custom to augment Diet No 2 by raw or underdone meat up to 8 ounces a day, in addition to liver soup. For this purpose raw meat is passed through a fine mincer and spread finely between two thin slices of bread. Diet No 3 is instituted from the third week onwards and adapted to convalescence according to the special needs of each, it is usually found necessary to persist with this until stools have become normal in size and of average consistency and colour. Convalescent sprue dietary should be nearly 4,000 calories daily, constituted as follows—

Milk, Benger's food, or Sprulac (2 pints)	800 calories
Rusks (10 oz.)	750 "
Sago (10 oz.)	876 "
Liver soup (16 oz.)	128 "
Chicken (6 oz.)	390 "
Two eggs (4 oz.)	180 "
Banana (2 oz.)	58 "
Orange (4 oz.)	60 "
<i>Extra</i> Underdone beef (6 oz.)	600 "



**High-protein diet** — It has long been known that soup made from liver is exceedingly well tolerated in sprue, and its virtues were appreciated by Manson long before the work of Minot and Murphy on the treatment of pernicious anæmia by a liver diet. Liver soup is made from fresh calves' liver, or from ox liver, and is prepared as follows —

Three quarters of a pound of fresh liver is finely minced, and immersed in a quart of water to which, when boiling, a small amount of tapioca or sago and some pepper and salt should be added. After simmering for two hours, the fluid is strained off and allowed to cool. The taste is much improved by adding stock prepared from beef or chicken bones.

Eight to sixteen ounces of this soup may be given daily, and to each cupful half a teaspoonful of Marmite may be added. For those who cannot tolerate underdone meat, its appearance and taste may be disguised by adding it to the soup.

It is to J. Cantlie (1906) that we owe the introduction of meat dietary in sprue. This is based on the Salisbury treatment and was originally prescribed for those who were unable to take milk. The meat was given in the form of raw meat juice (the expressed juice of 4 to 5 lb. of fresh lean meat) taken with a little water to allay thirst. When this was well tolerated, scraped underdone meat was added. The raw meat sandwich was made as follows —

A quarter of a pound of beefsteak freed from fat and gristle is cut into small pieces and passed through a fine mincer. Two thin slices of bread are toasted thoroughly. Pepper and salt are added and the meat is sandwiched between the pieces of toast and eaten slowly.

For those who cannot tolerate it raw, the meat may be slightly cooked in the following fashion —

One pound of tender undercut or beefsteak should be shredded finely and four tablespoonfuls of water added, with salt and pepper. This mixture should be placed in a steamer and stirred over the fire for seven to ten minutes until brown. It should then be served with a piece of dry toast.

A modification is the high protein dietary (N. H. Fairley) which has been found suitable for those patients with profound anæmia and signs of intestinal atrophy in whom flatulence and meteorism are pronounced. In such cases alimentary rest is the therapeutic ideal, and this can best be obtained by giving the patient a minimum amount of those food constituents which the small intestine fails to deal with adequately. Overloading of the stomach, also, is to be avoided. It is therefore rational to make protein the chief constituent, commencing with a diet of low calorie value, and gradually increasing the quantity while maintaining the high protein ratio. In this scheme five diets are employed, the calorie values of which increase progressively from 770 in No. 1 to over 3,000 in No. 5.

## DYSENTERIC DISORDERS

## DIET No 1

(Calorie value, 770)

8 a m — Underdone beef, 3 oz , juice of half an orange, and glucose, 2 drachms , rusks,  $\frac{3}{4}$  oz \*

12 noon — Soup, 4 oz + liver extract (equivalent to  $\frac{1}{2}$  lb ), underdone beef, 3 oz , rusks,  $\frac{3}{4}$  oz , juice of half an orange and glucose, 1 drachm.

6 p m — The same as at 12 noon

Protein fat carbohydrate = 10 03 12

Note — Where patients are very ill, two hourly feeds of meat and beef juice can be substituted

## DIET No 2

(Calorie value, 1,280)

8 a m — Underdone beef, 5 oz , rusks, 1 oz , calves foot jelly, 2 oz , juice of an orange, and glucose, 2 drachms

12 noon — Soup, 4 oz. + liver extract (equivalent to  $\frac{1}{2}$  lb ), underdone beef 5 oz , rusks, 1 oz , juice of an orange and glucose, 2 drachms

4 p m — Tea, 10 oz , milk, 2 oz

7 p m — The same as at 12 noon, with calves foot jelly, 2 oz

Protein fat carbohydrate = 10 03 10

## DIET No 3

(Calorie value, 1,820)

6 a m — Tea, 10 oz , milk, 2 oz

8 a m — Underdone beef, 6 oz , rusks,  $1\frac{1}{2}$  oz , calves foot jelly, 2 oz , juice of an orange and glucose, 2 drachms

10 a m — 1 baked apple, custard, 1 oz

12 noon — Soup, 4 oz + liver extract (equivalent to  $\frac{1}{2}$  lb ), underdone beef 6 oz , calves foot jelly, 2 oz , rusks,  $1\frac{1}{2}$  oz , juice of an orange and glucose, 2 drachms

4 p m — Tea, 10 oz , milk, 2 oz , baked apple, 1 oz , custard, 1 oz

7 p m — The same as at 12 noon

Protein fat carbohydrate = 10 032 13

## DIET No 4

(Calorie value, 2,200)

6 a m — Tea 10 oz , milk, 2 oz.

8 a m — Underdone beef 7 oz , rusks,  $1\frac{1}{2}$  oz , calves foot jelly, 2 oz , juice of an orange, and glucose, 2 drachms

10 a m — 1 baked apple, custard, 2 oz

12 noon — Soup, 5 oz + liver extract (equivalent to  $\frac{1}{2}$  lb ), underdone beef 7 oz , calves foot jelly, 2 oz , rusks, 3 oz , juice of an orange and glucose 2 drachms

4 p m — Tea 10 oz , milk, 2 oz , 1 baked apple, custard, 3 oz

7 p m — The same as at 12 noon, but only  $1\frac{1}{2}$  oz of rusk allowed

Protein fat carbohydrate = 10 034 13

\* The best are Heudebert Rusks or the Dutch variety Verkade's Grootte Beschuit.

DIET No 5  
(Calorie value, 3,020)

6 a m —Tea, 10 oz , milk, 2 oz , glucose,\* 2 drachms , rusks, 1½ oz , butter, 1 drachm , one scraped ripe apple or one fully ripe Canary banana (yellow ends)

8 a m —Underdone beef, 7 oz , rusks, 3 oz , calves foot jelly, 2 oz , juice of an orange and glucose, ½ oz , honey, 2 drachms , butter, 1 drachm

10 a m —1 baked apple , custard, 3 oz

12 noon —Soup, 5 oz + liver extract (equivalent to ½ lb ), underdone beef, 7 oz , calves foot jelly, 2 oz , rusks, 1½ oz , juice of an orange and glucose, ½ oz

4 p m —Tea, 10 oz , milk, 2 oz , glucose, 2 drachms , rusks, 3 oz , baked apple, 1 oz , custard, 3 oz (egg, boiled or poached, sometimes substituted), honey, 2 drachms

7 p m —The same as at 12 noon

Protein fat carbohydrate = 10 0 36 20

During convalescence a more liberal dietary is permitted, including cauliflower, marrow, celery, asparagus, tomatoes, and fruits. Red meats, chicken, and eggs are also advisable, but where carbohydrate intolerance has been a marked feature, small quantities of boiled potatoes and milk puddings are gradually introduced after convalescence has been well established.

On this dietary, increase in weight is not so rapid as it is on a diet containing more carbohydrate. The objects are to rest the bowel and to afford it a supply of blood which is richer in corpuscles and hæmoglobin. When this has been accomplished by the combined liver extract and high protein dietary, the ratio of carbohydrate is increased in a diet the calorie value of which is sufficient to maintain a steady increase in weight without the return of intestinal distension and gaseous stools.

**High-protein milk** —N H Fairley devised a milk powder which combines the advantages of a high protein dietary with the bland properties of milk. This high protein milk powder is now manufactured by Cow and Gate, Ltd, as Sprulac. It is prepared from fresh milk which is first treated by passage through a gauze and wire filter, is subsequently chilled and centrifuged to get rid of organic and inorganic debris and is then passed through a mechanical mixing apparatus and desiccated by the roller process at 120° C. For use in the tropics it is put up in tins in which the air is replaced by carbon dioxide. The chemical analysis of the powder shows —

Moisture	30 per cent
Fat	19.6
Protein	34.0
Lactose	45.0
Mineral matter	7.4

The calorie value per ounce is 125, and the ratio of protein fat, and carbohydrate is 10 0 3 13

\* Ordinarily 2 drachms of glucose are given twice daily. Insulin up to 6 units twice daily can be injected with this diet, and glucose can be increased according to requirements.

To many patients Sprulac is palatable, readily taken, and easily assimilated, and may be made very pleasant by the addition of coffee.

The Sprulac diet is made up as follows: One ounce of Sprulac in 8 oz. of water is given every 2½ hours for six feeds a day (7:30 a.m. to 7:30 p.m.), orange juice, calves foot jelly, baked apples, and custard being gradually added. Eventually underdone beef (4 oz.) and rusks are given also.

**Milk**—In former times the most successful method of treating sprue was by means of the milk cure. This was the treatment adopted by Manson, Van der Burg, Thun, and others. It may occasionally be useful, especially in young adults and the aged.

**Specific treatment:—Vitamin B<sub>2</sub>—Nicotinic acid and riboflavin.**—In acute recent cases of sprue, as well as in those of long standing, the author (1941) has recorded outstanding successes with nicotinic acid therapy based upon the principles expressed on p. 856. He has published the end results in a series of 24 cases. It is necessary that patients should be nursed strictly in bed because specific therapy is of little avail until the diarrhoea has ceased.

Nicotinic acid is given in tablet form (50 mgm.) in doses of 150–300 mgm. daily for 14–17 days, reinforced, whenever glossitis and angular stomatitis are prominent features, with tablets of 8 mgm. of riboflavin. The immediate and most striking effects of this form of therapy are upon the glossitis and rapid return of the taste sense. The subsidence of these irritating symptoms probably exerts a profound influence upon digestion and assimilation. The fiery redness of the tongue fades away within 24 hours and the appearance is restored to normal within 3 or 4 days. In glossitis of advanced sprue, with marginal indentations of the tongue and angular stomatitis, the addition of riboflavin is necessary to heal the angular excoriations. Probably further experience may suggest that larger doses of nicotinic acid may be necessary, while in those with intractable diarrhoea in whom absorption is impeded, injection of vitamin B<sub>2</sub> deep subcutaneously may be more advantageous. A soluble preparation for this purpose has been produced in *Pelonn* (Glaxo). This injection is followed within a few minutes by a notable "histamine effect".\* This treatment also favourably influences the intestinal manifestations. With the cessation of the diarrhoea (usually within four or five days) the stools gradually assume a normal size and colour within a period of 2–3 weeks. But the most gratifying change is the abatement of flatulence and meteorism, which are usually such persistent and distressing features. It is necessary to continue with nicotinic acid in reservoir doses (50 mgm.) for three months or even longer after the first course. The most striking testimony of the efficacy of this treatment has been that strict dietetic precautions appear to be no longer so necessary. All the patients in this series

\* This is characterized by a flushing of face, an intense feeling of heat, throbbing of the temples and a momentary increase of pulse rate.

have been able to eat a normal diet within six weeks and to resume their normal occupations. Four more recent cases can now be cited as examples of this treatment and are the more remarkable inasmuch as they both had suffered from unrecognized sprue for many years. At present it appears advisable to advocate nicotinic acid in close combination with liver therapy.

1—Male, aged 57 (May, 1941), sprue symptoms commenced in the Philippine Islands, had been in England two years with gradually progressing diarrhœa, glossitis and anæmia. Stools typical, never less than six daily. Anæmia customary megalocytic blood changes. Hæmoglobin 60 per cent. Red cell count 2,625,000. In bed 17 days, treatment with nicotinic acid 300 mgm daily plus total of 54 c c campolon liver injections. On discharge, hæmoglobin 90 per cent, red cell count 4,325,000. Stools normal in size and colour. Improvement maintained at least five months without further treatment. Increase in weight 14 lbs. Now leading normal life.

2—Male, aged 51 (May, 1941), 26 years' service in Malaya, had been one and a half years in England. Sprue symptoms for 14 years, loss of weight, glossitis, emaciation, megalocytic anæmia, with small thready irregular pulse and constantly recurring syncopal attacks, tetany and cramps. Hæmoglobin 75 per cent, red cell count 2,850,000. In bed 21 days, convalescence delayed by ischio rectal abscess. Treatment with nicotinic acid, 450 mgm daily, plus liver injections—total 54 c c "campolon". On discharge no diarrhœa or flatulence, normal sized, brown, solid stools. Hæmoglobin 85 per cent, red cell count 4,575,000 improvement in blood picture. Two months after, leading active life on war work, red cell count normal, eating full dietary. Increase of weight 14 lbs. No further treatment necessary.

3—Female, aged 59, three years in Bombay, 1922–1925, 15 years in England before onset of sprue symptoms. Seen in October, 1941. Then for 10 months had been suffering from typical sprue symptoms, loss of weight, 64 lbs. Flatulence and anæmia pronounced. Typical sprue tongue. *B. coli* cystitis. Condition had not been recognized, and many treatments instituted without effect. On nicotinic acid, riboflavin and liver treatment showed rapid improvement. In six weeks had increased 21 lbs. Stools formed and brown, appetite good. Red cell count 4,400,000. Writes in January, 1942, that she feels well, is at work and has made a miraculous recovery.

4—Male, aged 51, seen in October, 1941, 20 years in Assam, returned to England in 1938. Sprue symptoms for one year. Sore tongue with aphthæ, emaciation, meteorism, anæmia, considerable dilatation of stomach, low blood pressure (110/65), œdema of legs, tachycardia pulse 48. Treatment in bed for 17 days, nicotinic acid, 450 mgm daily, and riboflavin. Anahæmin injections 4 c c daily for seven days. Marked febrile reaction to treatment. T 103° F with sweats. Improvement rapid and striking. Disappearance of all sprue symptoms within seven days, return of appetite, formed brown motions, increase of weight (26 lbs within two months), blood count normal, hæmoglobin 94 per cent. Is now on normal diet, has had no more sprue symptoms and feels well.

**Fruit.**—The value of fruit in the treatment of sprue has long been recognized, and in the popular opinion sprue is quite an agreeable disease, which can be treated successfully by a diet of strawberries. Some authorities have held that fresh fruit, or even extracts, exerts an almost specific effect,

it was, therefore, formerly the custom to feed sprue patients on this fruit even during the winter season, when it was obtainable. The author, however, is convinced that, though strawberries are beneficial as an adjunct to the sprue dietary, they are only so when ripe at the proper season. Almost all fresh fruit is of value in the treatment of sprue, probably on account of the vitamin content.

The strawberry treatment commences with two or three given with each feed, if found to agree, the number is increased until two or three pounds are taken daily. Preserved strawberries and strawberry jam have also been employed, but they do not appear to exert the same effect as does the fresh fruit. The author has met with patients who have subsisted entirely, during the height of the season, on a diet of strawberries, and have succeeded in eating as much as 10 to 13 lb. of strawberries daily, but usually moderate amounts ( $\frac{1}{2}$  lb. a day) of the fruit fulfil the purpose of a natural laxative. Fresh raspberries and blackberries are almost as well tolerated as strawberries. At other seasons of the year when these fruits are not available, a Canary banana is a welcome adjunct to the diet. Sometimes a dietary of fresh tomatoes is beneficial.

Bael fruit (*Aegle marmelos*) was introduced by Fayrer for the treatment of this disease, and appears to exert a beneficial effect in those countries in which it can be obtained in a fresh state, i.e., Ceylon, India and the tropics generally. It is advisable to give one large or two small fruits during the day. The ripe pulp should be scraped out of the hard shell and eaten with sugar and cream, or mashed into the consistency of gooseberry fool, strained through muslin, mixed with gelatin and made into a jelly, the flavour of which is much improved by a wineglassful of sherry. These fruits have been imported on ice to London during recent years, but their value is then questionable as they decompose so quickly in this climate. It is still more doubtful whether extracts of the dried fruit are efficacious. There is, however, an efficient bael fruit paste now on the market which can be obtained at one rupee a pot.\*

Papaya (*Carica papaya*), also known as the pawpaw or mummy apple, which contains the very potent ferment known as papaine, can be obtained in nearly every tropical country, and is also imported into England,† but unfortunately, it does not keep long. The pulp is quite agreeable in taste but somewhat insipid; it is easily digestible, and some patients thrive exceedingly well upon it.

Other fruits, such as baked apples and stewed plums, are useful. Bottled blackberries (especially Southwell's) are of value, and Libby's tinned strawberries and blackberries can also be recommended.

For the constipation that follows the acute stage of sprue, boiled onions, spinach, vegetable marrow, and especially, cauliflower stalks, may be used with great success.

### MEDICINAL TREATMENT

**Care of the mouth and tongue**—Much can be done (in addition to meotinic acid) to ameliorate the soreness and great distress caused by the stomatitis of sprue. The first measure is a mouth wash, for the

\* The U.P. Stores, 15 Lindsay Street, Calcutta.

† Lever and Sherlock, Kingston, Jamaica, and The Army and Navy Stores.

mouth should be washed out thoroughly after each meal. The least irritating is potassium chlorate 2 drachms to the pint of rosewater glycothymolin or the proprietary article known as Lavis mouth wash.

In certain cases where the saliva is very acid neutralization of this by an alkaline mouth wash for instance Phillips's Milk of Magnesia 1 drachm to half a tumblerful of water is often followed by great relief. In other cases where the mouth is septic the author has found hydrogen peroxide washes to be extremely effective. For this purpose the stock solution of hydrogen peroxide 10 volumes is taken and half a teaspoonful is added to half a tumblerful of water and the mouth thoroughly rinsed. When the patient becomes tolerant increasing strengths may be used.

*Glauramine*,\* a flavine product (diphenyl methane) yellow and of slightly bitter taste has an effect in healing the mouth lesions of sprue. One drachm (one teaspoonful) in half a tumblerful of water is used as a mouth wash twice daily. The yellow colour can be effectively removed from the tongue and lips by application of a cloth moistened with a little soap and water.

The mouth and tongue are swabbed with the standard preparations of glycerin and borax and if there is great pain 1 or even 2 per cent cocaine may be added. The author has found that sucking *euphagin* tablets also alleviates the pain. These contain para amino benzoic ethyl ester and menthol and have the effect of anæsthetizing the tongue. Painting the ulcers with equal parts of crystallized carbolic acid and camphor is advocated and a 1 in 1000 solution of optochin is also recommended. For dysphagia 5 to 10 drops of 1 in 1000 adrenalin in water every four hours is said to give relief.

**The treatment of diarrhœa**—The best plan to combat the diarrhœa of sprue is to administer a small quantity of some potent aperient such as castor oil 2 or 8 drachms in order to clear out the bowel after which Batavia powder (*Pulv. Bataviæ co.*) checks the diarrhœa. This is a modification of the proprietary powder known as Peter's specific, used by Manson, Canthie and other early observers. The powder is given suspended in milk or water in doses of 1 teaspoonful (1 drachm) a day in very obstinate cases of diarrhœa as much as 8 drachms (1 drachm three times daily) is given but during convalescence it is useful in wafer cachets of 15 grains four times daily. Although mythical properties have been ascribed to this powder equally good results are obtained with Crooke's colloidal kaolin in drachm doses while for nocturnal diarrhœa a bismuth and magnesia mixture (bi<sup>o</sup> oxycarb 15 grains mag carb pond 15 grains) with chloroform water may be used. The author is convinced that unless the diarrhœa is efficiently checked no response to specific treatment as for instance with nicotinic acid (see p. 392) can be attained.

**Peri-anal irritation or eczema** may be very troublesome and the parts must be kept clean with a diluted solution of potassium

permanganate, followed by a dusting powder of equal parts of talc and boracic acid. The following ointment gives relief —

R Orthoform	40 gr
Zinc oxide	120 gr
Starch	120 gr
Paraffin ad	1 oz

**Flatulence and meteorism** — Persistent flatulence and meteorism are distressing and may be made more so by unsuitable diet, it may be for instance due to too much milky or sloppy food, so that the high protein régime has to be adopted. Pituitary extracts are most useful especially pitressin ( $\frac{1}{2}$ –1 c c), the injection of which is followed by relief when this cannot be obtained. ordinary pituitary extract may be given. Charcoal compounds are also efficacious, e.g. charcoal biscuits (one three times daily) or a very good preparation known as Charkoalm (Allen and Hanbury).

The following prescriptions are sometimes useful —

R Sp æther nitros	15 min
Sp ammon aromat	15 min
Aq menth pip ad	$\frac{1}{2}$ oz
Occasionally	

R Ol menth pip	16 min
Mag carb	1 dr
Cret prep	10 gr
Sod bicarb	2 dr

One teaspoonful in  $\frac{1}{2}$  tumblerful of water

R Acid sulph aromat	$\frac{1}{2}$ oz
Ol cajuput	40 min.
Ext hamatoxyh	3 dr
Sp chlorof	1 dr
Syr zingib	3 oz

One drachm in  $\frac{1}{2}$  tumblerful of water whenever necessary

**Extreme meteorism and abdominal distension** — In advanced cases with atrophy, dilatation of the small and also of the large intestine takes place so extreme that it resembles Hirschsprung's disease. These cases are very difficult to treat, as the distress caused by the gaseous distension is considerable. They require very careful dieting and restriction of the amount of fluid. The author has found that the best line of treatment is a combination of pituitary injection (pitressin  $\frac{1}{2}$ –1 c c) and high colonic lavage with hypertonic saline solution (2 pints). This is the one condition in which mechanical lavage of the bowel appears to do good. In other cases of sprue it is contra indicated.

Rectal injections of warm olive oil (4 to 8 ounces) are also useful. In extreme cases a rectal tube may be used with success. A glycerin suppository may also be helpful.

**Anorexia** — The loss of appetite and distaste for food, which is



such a feature of acute cases, usually responds to injections of vitamin B<sub>1</sub> (Benerva Roche), 5 milligrammes daily for five days

**Constipation**—Constipation following the acute phase of sprue is frequently almost as difficult to overcome as is diarrhœa. Often hard scybala form in the sigmoid loop and become impacted causing extreme pain, in their passage along the bowel, also, they may excoriate the mucous surface, causing intestinal hæmorrhage. The best aperient in these cases is undoubtedly castor oil given in drachm doses in liquid form or in cachets. In extreme cases it may be necessary to give an enema of warm olive oil (10 ounces) or even to remove the scybala from the rectum by means of the fingers.

As a general aperient, preparations of petrol and agar, such as Petrol agar (Red Label) in doses of 1 to 2 drachms at night, have the desired effect, and Agarol is almost as effective. Normacol is also useful, as is also Allen and Hanbury's preparation, Logel. When the constipation is accompanied by extreme flatulence, hot applications to the abdomen or the immersion of the patient in a bath is often useful.

**Treatment of tetany and cramps**—Cramps of a group of muscles, especially those of the feet and legs, are almost invariable concomitants of a well marked case of sprue. They, and also tetany, which is but a more extreme expression, are due to deficient calcium, but when it is reduced below 8 mgm per cent the administration by the mouth is followed by alleviation. The following preparations of calcium are recommended. Kalzana, two tablets three times a day, and calcium lactate, 10 grains, three times a day. It may be given in a mixture, as follows—

R Calc carb	75 gr
Acid lact	200 min
Aq chlorof ad	8 oz

Mix calc carb præcip with 3 oz of tap water. Dilute acid lact with about 2 oz aq chlorof (double strength). Mix gradually the two solutions. Stir well until the effervescence ceases. Make up to 8 oz with aq chlorof double strength. One ounce of this mixture contains approximately 30 gr of calcium lactate.

Calcium gluconate (Sandoz) injections (10 c c) are also useful in extreme cases.

The realization that sprue is accompanied by a calcium deficiency led H. H. Scott, in 1923, to suggest the routine treatment of this disease by means of calcium and parathyroid. He advised that the calcium be given in the form of lactate in doses of from 10 to 15 grains three times a day, coupled with the administration of tablets of extract of parathyroid (Parke Davis & Co), 1/10 grain, two at night. These should be continued in full doses until the fifth week, reduced, and stopped altogether at the end of six weeks.

**Treatment of sprue anæmia.**—In the early stages anæmia responds rapidly to dietetic treatment, and this, when necessary, can be reinforced

by iron preparations. In more extreme degrees, and especially when accompanied by hypochlorhydria the treatment follows the same lines as for pernicious anaemia. Diluted hydrochloric acid, 20 to 30 minims in orange juice, is given immediately after meals, but in the acute stages some cannot tolerate the burning of the tongue and mouth caused by this acid and hydrochloric acid is then exhibited in the form of tablets of acidol pepsin or betaine hydrochloride, 2 three times a day.

In extreme anaemia blood transfusion has been resorted to with success. Care should be taken that the blood is carefully matched and that there is no auto-agglutination. Large transfusions (above 800 c.c.) must be avoided, it is probably better to give several small than one large one. The author in 1927 published a series of cases in which recovery from extreme anaemia as well as from all sprue symptoms took place after a blood transfusion. The deductions he arrived at from the study of five cases was that the effect was due not so much to mechanical replacement of the destroyed blood corpuscles, as to stimulation of the blood forming organs. In two instances, more than one blood transfusion proved necessary to obtain the desired result.

*Liver therapy*—The beneficial effects of liver soup in sprue have already been noted. Since the work of Minot and Murphy in 1926 it has been customary to reinforce this by the administration of liver extracts by the mouth but this is very expensive treatment most patients cannot afford it, and it is by no means so efficacious as the injection method. Favourable results in the stimulation of reticulocytes take place after the intramuscular injection of liver extracts. One of the best preparations is Hepatex (P. A. F., B. D. H.), of which 1 or 2 c.c. are given daily for ten days in which period a reticulocyte rise usually takes place. Campolon (Bayer) 4 c.c. on alternate days for at least twelve injections, is followed by gratifying results\*. The first injections are somewhat painful at the site of inoculation but the pain gradually wears off as further injections are given. This method has the advantage of being considerably cheaper than the oral liver extract. In cases in which there is no satisfactory response to this method of treatment and in cases in which the anaemia is, as occasionally found of the microcytic type iron extracts, e.g. ferrous sulphate tablets, 5 grains two at night, or hæmatine plastules (Wyeth) are advantageous. The scale preparation of ferri et ammonii citras in 80-grain doses daily is extremely useful on account of its ready solubility.

*Additional measures*—In order to promote metabolism and to increase the appetite in recalcitrant cases, small doses of insulin have been found useful commencing with one unit a day and gradually working up to six.

Massage and passive movements are of considerable benefit, especially in men who have been accustomed to hard exercise. They certainly

\* In extreme cases as much as 6 c.c. can be tolerated

appear to improve the nutrition of the tissues and promote contentment of mind and body. Massage of the abdomen however should be deferred until all the more urgent symptoms have subsided. then especially in severe constipation it may prove of considerable value.

*Heliotherapy*—Heliotherapy either by exposure of the patient to the direct rays of the sun or by application of ultra violet rays to chest and abdomen has a place in the therapeutics of sprue.

### CONVALESCENCE

The treatment of convalescence in sprue is an important matter and in order to avoid relapses it is necessary that the patient should reside in an equable climate. Extremes of heat and cold especially winds accompanied by rain are likely to produce relapses of diarrhœa. Those people who can afford it are well advised to spend the winter out of England especially in the Canary Islands or Madeira where a continuous supply of fresh fruit and particularly tomatoes can be procured. Egypt and North Africa are on the whole unsuitable for sprue patients on account of the extremes of temperature and also because of the irritating sand and dust. Those who have to remain in England should winter in some mild health resort such as Torquay or Paignton or other parts of Devonshire Cornwall or the Isle of Wight. The East Coast is particularly unsuitable in the winter and spring months while sprue patients of Scottish origin should be discouraged from returning to their homeland until the autumn.

For those whose physical condition permits it walking is by far the best exercise during convalescence this should be persisted in should be graduated and should be pressed to the point of slight fatigue but extreme fatigue must be avoided. Mild golf appears to be useful. Motor trips are apt to bring on chills and diarrhœa. Should the patient's occupation involve strenuous physical exertion he must gradually train his body for at least six months before returning to full duties.

A reservoir dose of Campolon (4 c.c.) *Peruæmon forte* Anahæmun or some other liver preparation given intramuscularly or deep subcutaneously twice weekly is desirable for several months.

The question of diet in convalescence always arises. The more one sees of this disease the more is one convinced that this is a matter of importance and that the longer the restrictions of diet are persisted in the better is the ultimate outlook. Convalescent diet consists of all reasonable articles of food with the exception of coarse vegetable such as cabbage broad beans carrots and turnips of potatoes and of ordinary butcher's meat. Cheese rich cakes rich sauces pastry and condiments are also definitely contra-indicated. Most forms of alcohol are to be avoided particularly such fermented liquors as beer and stout but for those who are accustomed to it one whisky and water may be allowed at night. The meals should be light over eating must be avoided and supper should be the lightest meal of the day and

taken before 7.30 p.m. Any tendency to constipation must be checked by the addition of more fruit and by taking Pétrolagar. Plenty of chicken and fruit should be eaten and all fatty preparations and starchy puddings avoided. Vegetables such as tomatoes and cauliflower appear to be well tolerated, but such starchy foods as white bread, rice puddings, and beans are not.

## CONVALESCENT DIET

*Breakfast*

Porridge made from	
Quaker Oats	$\frac{3}{4}$ oz
Milk (or Sprulac)	$\frac{1}{2}$ pint
Sugar	$\frac{1}{2}$ oz
1 Egg lightly boiled	
Toast	$1\frac{1}{2}$ oz
Tea (very weak)	

*11 a.m.*

Warm milk or Sprulac	$\frac{1}{2}$ pint
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*Lunch*

Liver soup	12 oz
Boiled fish	6 oz
Chicken	4 oz
or Rabbit	4 oz
Spinach	3 oz
or Veg. marrow	$3\frac{1}{2}$ oz
Peas	$1\frac{1}{2}$ oz
or Cauliflower	4 oz
Milk pudding	$\frac{1}{2}$ pint
Baked apple	6 oz
or Banana	3 oz

*Tea*

Toast	3 oz
Madeira or sponge cake or biscuits	3 oz
Weak tea	

*Dinner*

Brains	4 oz
or Sweetbread	3 oz
Calves foot jelly	3 oz
Banana	3 oz
Arrowroot	$\frac{1}{2}$ pint

**Return to the tropics**—The return of the sprue patient to the tropics is always a vexed question. Unfortunately the balance of evidence goes to show that when the disease has become well established even if complete recovery appears to have taken place on return to the tropics relapse is apt to occur sooner or later. Often the ruling on this point appears to be a very harsh one as it may mean cutting short the career of young and promising officials. It is difficult to formulate definite rules. The author's own impression, the result of considerable experience, is that the physical and mental state of the patient should be taken as a guide, due regard being paid to his occupa-

tion and age Those under thirty can be said to recover from sprue completely, and there are numerous instances in which men and women have served for many years in India and the East after suffering from a severe attack It is otherwise in those over fifty, on no account should they be permitted to return if it can be avoided, because in more elderly people, when relapses have taken place, intestinal atrophy may attain a degree from which recovery is impossible

There appears to be also definite danger in returning to the locality where the disease was originally contracted—Bombay for instance Patients, on the other hand, may return to some up country station in India and, if careful about their dietary, may remain free from symptoms The tendency to relapse does not appear to be brought about solely by the tropical climate, because patients who originally contracted their disease in India, may thereafter reside in East and Central Africa with impunity In the author's work on sprue in Ceylon, some twelve cases are cited of people who continued to live on the island for twenty years or more after recovery from sprue

**Prognosis**—In the average case prognosis is good, provided that the nature of the disease is adequately recognized and the necessity for strict dieting is appreciated Since these essentials have become more widely known, and their due value assessed, the writer has found that the hopelessly atrophied cachectics, with capacity for absorption totally destroyed, are no longer encountered The impression gained from older textbooks is that sprue is necessarily a fatal disease, this is, of course, by no means true

The prognosis depends a great deal upon age The outlook in those below the age of thirty is distinctly good, however bad the symptoms may be, and the patient can be assured of a permanent restoration to health if he continues to live in a temperate climate The prognosis is by no means so favourable in cases of relapsing or recurrent sprue in persons over fifty, especially when the sprue commences, as so frequently, as an aftermath of long arduous residence in the Far East But it is a great mistake even then to consider the case hopeless An optimistic attitude on the part of the patient, as well as on the part of the doctor, constitutes half of the battle

It is difficult to state the mortality rate of sprue under modern conditions, but it is somewhere about 7 per cent In elderly people the sprue process may not be the actual determining cause of death G Carmichael Low has given the following table in an analysis of his 150 cases

Cured	22
Satisfactory	60
Improved	22
Not improved	16
Died	10
Unaccounted for	20

In the author's series, the mortality rate has been 15 per cent,

excluding those moribund on admission. The prognosis has greatly improved since the introduction of Cumpolon, other liver injections and nicotinic acid.

**Prophylaxis**—While the true aetiology of sprue remains obscure it is very difficult indeed to lay down definite instructions for its prophylaxis, but certain facts emerge and the author feels justified in setting forth his personal views. Undoubtedly, prolonged residence in an endemic zone without regular leave to a temperate climate does predispose to the development of sprue in the European. To escape its ravages, regular annual leave to a cooler atmosphere is necessary, a succession of hot weathers in the plain of India must be regarded as a definite factor in causation.

**Housing and sanitation** have been found to affect the incidence and nowhere does this appear to have been more adequately recognized than in Ceylon where erection of modern bungalows with effective sanitation and conveniences has undoubtedly lessened the incidence.

Due attention must be paid to the effects of *previous disease* which as we have seen exerts a predisposing influence in sprue. The most important diseases from this aspect are malaria, dysenteries and hill diarrhoea and all that appertains to their prophylaxis applies also to sprue. In women repeated pregnancies and parturition are a debilitating factor; this was recognized long ago by Patrick Manson and is now realized in India and indeed wherever sprue occurs.

**Personal habits**—Whether personal habits, such as over eating and drinking or the habitual ingestion of any particular article of food such as hot curries lead to changes in the intestinal tract and to sprue is still unsettled. Possibly the frequency with which sprue formerly occurred in veterans, the devotees of club life was in part due to chronic alcoholism. This led Manson to remark that sprue might be regarded as the past participle of the verb 'to spree'. There is however some evidence that alcohol is to be regarded merely as a debilitating factor so rendering the subject more liable to infection. There is at present no evidence that food per se whether frozen or contaminated, exerts any influence upon the production of sprue.

### HILL DIARRHOEA

This is a form of mild diarrhoea accompanied by flatulent dyspepsia and the passage of copious liquid, pale and frothy stools. In many respects it resembles the early stages of sprue with which it is closely associated and may often constitute the starting point of that serious disease. It occurs principally in Europeans visiting the hills after residing for some time in the hot lowland or tropical countries especially India.

**History**—A. Grant (1854) originally described hill diarrhoea as occurring at Simla at an elevation of 6 500 to 8 000 feet. It was then considered to be a source of serious inefficiency, and the cause of invaliding among the troops stationed at Simla. At first it was

regarded as a form of scurvy. A Crombie in 1880 described a very severe epidemic at Simla in which about 75 per cent of the population were attacked. He regarded the disease as a disorder of the liver brought about by the unaccustomed low temperature of high altitudes after residence in the hot plains of India. He pointed out that a similar affection sometimes showed itself in the highlands of Europe. J. Duncan at a later date put forward the hypothesis that this peculiar form of diarrhoea was due to the presence of mica in drinking water derived from laterite rocks. This hypothesis was subsequently supported by Dyson.

**Geographical distribution**—It is noted that in India at an altitude above 6 000 feet an atmospheric saturation with water vapour is apparently particularly favourable to the development of hill diarrhoea. Outbreaks begin and end with the rains. In certain years the disease is apt to assume an epidemic character, thus in 1880 50-75 per cent of the European population were affected, three quarters of these within one week. In some years hill diarrhoea is less prevalent than in others.

According to Pock Steen (1937) a similar affection occurs in the highlands of Java locally known as Bandoeng Sprue. It is met with at a more or less definite height on the Preanger plateau. He suggests the possibility of a suprarenal insufficiency resulting in disturbance of lipid and carbohydrate metabolism as explaining the low blood pressure, low blood sugar and increased susceptibility to bacterial toxins. Commonly the diarrhoea is a sequel to an acute attack of bacillary dysentery. The association of this diarrhoea with all the manifestations must be borne in mind.

**Ætiology and pathology**—It is difficult to say what the precise factors are which determine the onset of this disease. The low barometric pressure associated with great elevation above sea level may be a favouring circumstance. Damp seems to be indicated by the fact that the disease occurs principally during the rainy season while chills after exposure to the high temperature of the plains have possibly an important share. There appears to be some interference with the functions of the liver and this is borne out by the dyspepsia and the character of the stools. Possibly a portion of the small intestine concerned in digestive as well as in absorptive processes is implicated for hill diarrhoea appears to be something more than catarrh of the bowel. Hypochlorhydria is common. Physiological causes may play a great part in bowel disturbances in the tropics with particular effects on the hepatic functions and the excretion of bile as can readily be understood when we take into account the drastic changes entailed in the rapid removal from the hot steamy plains to a cool and even chilly station. There is an urgent need for further investigation of the physiological consideration here involved for a complete understanding of the true ætiology may shed light on the genesis of the steatorrhoeas.

**Symptoms**—Without any obvious cause the patient who appears

to be in general good health, becomes attacked soon after arrival at a hill sanatorium with looseness of the bowels, which comes on regularly every morning between three and five o'clock. The diarrhoea is sudden and imperative and the motions passed are remarkably copious, very watery in some instances and pasty in others. They are pale and frothy, and have been compared to recently stirred whitewash. The passage of the stool is attended with little or no pain and is followed with a great sense of relief. Usually half a dozen or more of such stools are voided before 11 a.m., but after that hour the diarrhoea is in abeyance for the rest of the day, and the patient may go about his duties feeling perfectly normal. Thus, the distinctive features of this form of diarrhoea are the regularity of its recurrence every morning, its cessation after a certain hour, and the absence of colouring matter in the stools. There is also a very considerable amount of flatulence. The abdomen is blown up like a drum, so that the patient becomes conscious of unpleasant peristaltic movements, associated with a sensation that some chemical process is proceeding inside.

Occasionally cases are met with in which the stools become very pale, although there is no actual diarrhoea, such cases are frequently encountered among passengers on big liners emerging from the tropical heat into the cooler atmosphere of the Mediterranean. It is most necessary that this purely temporary affair should not immediately be regarded as the manifestation of the more serious disease of sprue, although, as has already been pointed out, the one may lead, after a considerable period, to the other. Pock Steen has shown that 'pseudo-allergic' symptoms such as bronchial catarrh and hay fever, may precede the attack but tend to disappear as soon as the sprue-like diarrhoea manifests itself. Urticaria is frequent. Nervous phenomena are also noted accompanied by low blood pressure and tachycardia. Myasthenia and fatiguability are common sequelae.

**Treatment**—The attack of hill diarrhoea is usually slight and yields to simple remedies. As recommended by Crombie and endorsed by nearly every physician of experience since his day, the diet should consist almost entirely of milk. The patient should be put to bed, clothed warmly, and given one teaspoonful of liquor hydrargyri per chloridi in water, fifteen minutes after food, two hours later he is given 12 grains of pepsin lactopeptin or some other digestive ferment. Pock Steen recommends calcium lactate in large doses. When the diarrhoea persists after this treatment, the only method which pronoses success is that the patient should be sent down to a low country where the climate is warmer and there are no sudden changes of temperature.



## CHAPTER XXII

### IDIOPATHIC STEATORRHŒA, CÆLIAC DISEASE, PANCREATOGENOUS STEATORRHŒA

#### IDIOPATHIC STEATORRHŒA AND CÆLIAC DISEASE

**Synonyms**—Cœliac Disease, Gee's Disease, Gee Herter Disease, Gee Thaysen Disease, *Die Coeliacæ* (German)

**History.**—In 1888 Samuel Gee published a description of the 'Cœliac Affection' in which he gave a clear description of a steatorrhœa occurring in patients of all ages, but especially in young children. He gave there a good picture of the pale, bulky, offensive stool of cœliac disease, but as he appears to have included a number of cases of patients who had previously resided in India, it is probable that he regarded this disease as indistinguishable from tropical sprue.

In 1908 C. A. Herter published a book on 'Infantilism from Chronic Intestinal Infection,' in which he associated the maintenance of a fair degree of mental development with arrest of the bodily development, marked abdominal distension and a moderate degree of anæmia. He further commented upon the occasional occurrence of rickets, and the changes observed, though rarely, in the tongue, which may be red with swollen papillæ. In his biochemical studies, C. A. Herter showed that there is a disturbance of calcium balance and he further demonstrated that 80–40 per cent. of the fat in the stool was in the form of fatty acids. This fat loss was not due, he considered, to diminished power of fat splitting but to a failure of absorption. The retardation of development he attributed to insufficiency of food absorbed from the digestive tract and the failure of calcium absorption to calcium loss in the stools.

In 1909 the condition was described again by O. Heubner in Germany, and in that country it is frequently referred to as the Herter-Heubner disease. The monograph of K. Hansen and H. v. Staa (1936) clearly indicates that the disease in Germany is essentially the same as that described by E. H. Thaysen in Denmark and T. I. Bennett, D. Hunter and J. Vaughan in England.

It is probable that cœliac disease in children which manifests itself by digestive disturbances and diarrhœa is the same as steatorrhœa in adults. This aspect has been specially studied by L. G. Parsons and A. H. Miller. The pathological changes in the intestinal tract have been studied in Austria by H. Lehndorff and H. Mautner (1937).

The resemblance of this condition to tropical sprue has been com-

mented upon since the time of Gee. In recent years E. H. Thaysen has been the chief exponent of this view which he has summarized employing a wealth of material in his book on "Non Tropical Sprue" (1932). He states unequivocally that tropical sprue and idiopathic steatorrhœa are one and the same disease.

The association of tetany with steatorrhœa has been widely commented upon and was specially studied by F. Langmead in 1911. Coeliac disease in children has been found, especially by L. G. Parson, and A. F. Hess to be the cause of rickets. The hæmatological features of idiopathic steatorrhœa have been studied by G. Fanconi (1928) and E. H. Thaysen (1931).

It has become clear that coeliac disease is not confined to childhood, but may make its first appearance in adolescence or may press itself on our attention for the first time in adult life even, it may be, in old age. It is also to be noted that the disease may be characterized by emaciation, fatty diarrhœa, infantilism, tetany, osteomalacia, rickets, a definite anæmia, and megacolon. Pellagrous lesions on the skin have been noted in advanced cases (Bennett, Hunter and Vaughan, 1932). The general affinity of this group of steatorrhœas to tropical sprue is clear, and the conceptions underlying this idea have already been set forth (p. 841) but certain additional information regarding the ætiology of the group has come to light. T. Verzar and L. Laszt (1936) have now been able to show that vitamin B<sub>2</sub> (riboflavin) is a respiratory enzyme connected with flavin phosphoric acid and that its production can be prevented by mono iodoacetic acid. In animals so poisoned, other processes connected with phosphorylation are also inhibited. Thus steatorrhœa and osteoporosis developed and the picture became that of coeliac disease. It therefore appears possible that this group of diseases can best be explained as an effect of inhibition of phosphorylation through decreased production of adrenal cortical hormone.

### CELIAC DISEASE IN CHILDREN

Coeliac disease in childhood (also known as chronic intestinal indigestion and intestinal infantilism) has now become a well recognized entity in pediatrics, and has been the subject of much study in recent years. The onset of this affection, now generally recognized as an inborn error of metabolism, usually occurs in children between one and five years of age, it may, however, remain unrecognized till the child has attained the age of seven or more. Among fifty four cases analysed the age of onset varied between four months and sixteen years. It is apparently a much more common condition in the British Isles and in Germany than in the United States, L. C. Holt and R. McIntosh state that it occurs only once in every 1,500 admissions to the children's hospital in Baltimore.

**Ætiology**—The parents may volunteer the information that the child has exhibited difficulty in digesting milk from the commencement. Both sexes are equally liable to coeliac disease, but heredity appears

to have a definite influence—a matter which certainly requires fuller investigation. Fanconi has pointed out that the disease is more frequent in communities where the infant mortality is low.

**Pathology**—In all cases in which investigations have been carefully conducted no characteristic pathological change has been revealed.

No satisfactory explanation of the difficulty in fat absorption is at present available. There is no defect in fat splitting, and no true steatorrhœa, such as the passage of fat droplets, no changes have been found in the pancreas at autopsy, nor has any evidence of endocrine deficiency been forthcoming. H. Lehnendorff considers that the changes seen at autopsy are consequent upon diarrhœa and malnutrition. The loading of the mesentery with fat has been commented upon.

H. Thursfield and D. Paterson (1934) have suggested that the disorder may be due to some loss of action of bile salts. There is a disappearance of glycogen from the liver as the result of chronic disturbance of nutrition. Gastric achylia has been found to be the exception rather than the rule. The fasting blood fat is low, but after a fat meal it fails to rise to the normal extent, so that a flat lipœmic curve is obtained. There is therefore a failure of fat absorption.

The fasting blood sugar may be subnormal, so that a flat low sugar curve is characteristic. The explanation of this curve as of that in sprue, is still in doubt, but there is good reason to believe that this metabolic defect is similar to that of rickets in small infants. It seems that the patient is unable to absorb an adequate amount of vitamin D, though a corresponding vitamin A deficiency has not been noted in coeliac disease. E. Badenoch and N. Morris have shown that the height of the blood sugar curve after ingestion of glucose increases with age, but flat blood sugar curves are not pathognomonic of coeliac disease since they are present also in hypothyroidism and in marasmus. Simultaneous administration of fat with glucose flattens the blood sugar curve even in healthy children. Children with coeliac disease are more sensitive to the effects of insulin than are normal children.

Injection of anterior pituitary extract raises the level of the fasting blood sugar and causes a short improvement in the absorption of fat. The radiographical appearances according to R. Golden (1941), resemble those of idiopathic steatorrhœa in adults (p. 418). Similar changes were recorded by E. Spriggs (1937) in a fatal case.

**Symptomatology**.—The child suffering from coeliac disease presents a wan, thin, and sallow appearance. There is emaciation of the body, legs, and arms, the face being usually less affected. Dark rings are noted under the eyes. The abdomen is prominent and distended. Such children show marked nervous symptoms: they are irritable, extremely difficult to manage, and easily fatigued. Development is generally retarded and mentality is slow. In older children if the disease persists, there is infantilism and retarded sexual development.

The gastro-intestinal symptoms are attributable to errors in fat absorption. The stools are loose, pale and copious, but in number

may not exceed one or two daily. In severe cases they assume a frothy and offensive character and the bulk may then be extreme. The excess of fatty acids is responsible for the stench of the excreta, and possibly also for the secondary enteritis. Exacerbation of symptoms occurs at irregular intervals and appears to be due to any increase of fat in the dietary.

The abdomen is distended, the meteorism being due, mainly, to flatulence. The muscles are flabby and the lower edge of the liver may be palpable. In some cases megacolon may develop, especially in those in whom diarrhoea is not severe. The appetite is poor and there is usually a natural inherent reluctance to take fats and milky foods. If the child is forced to eat these, vomiting may occur. Some of these children are so extraordinarily sensitive to fat in food that a small amount may precipitate an attack of fever and diarrhoea.

In severe cases of coeliac disease evidence of interference with the calcium and phosphorus metabolism may appear in defective bone development, e.g., in osteoporosis and rickets. The bony changes have been specially studied by L. G. Parsons (1933), who regards the rickets as of the late type. Tetany, with Trousseau's and Chvostek's signs, has been noted in these cases. Anaemia may be a secondary factor, and appears to follow the same lines as in steatorrhoea of adults, that is, it may be simple hypochromic anaemia responding to iron or a megalocytic hyperchromic anaemia responding to liver or to yeast (marmite) therapy. On rare occasions there is a type resembling 'Cooley's' anaemia—an erythroblastæmia, which responds to treatment with iron.

A low degree of nocturnal fever associated with night sweats and persisting for months is common. Less frequently, bouts of high fever may occur, preceded by loss of appetite, coated tongue, and sallowness.

Two main types of coeliac disease in children can be differentiated. The first is associated with diarrhoea; in the second the symptoms are much milder, but the stools, though formed, are large, pale, and bulky.

No changes in the tongue or buccal mucosa have been noted.

*Progress of case*—The ability to absorb fats may increase gradually, and abdominal disturbances may diminish as growth develops. Thus in some the ability to absorb fat is regained, while others, recognizing this inability, automatically avoid fats for the rest of their lives. The megacolon developed in infancy may persist in adult life.

Cases in which there is extreme wasting and diarrhoea, and especially those in which tetany develops, are usually fatal. The mentality, which is slow, with loss of power of concentration, may improve after puberty and on a suitable dietary. D. Hunter and others have remarked that children with chronic coeliac disease may develop signs of pellagra.

The writer has encountered three cases of coeliac disease in small boys of European parentage, ranging in age between 2½ and 7½ years. One hailed from India, one from Hong Kong and the third from Malaya. In each

the illness apparently commenced as a sequel to an acute attack of dysentery, presumably bacillary. The chief features which impressed themselves on the mind were the extremely irritable temperament, the distended abdomen, the capricious appetite, and the large, offensive clay coloured stools. The improvement in mind and body which followed appropriate treatment with a fat free dietary was both rapid and striking.

**Diagnosis**—The diagnosis is not difficult to make in a typical case. Coeliac disease has to be distinguished from rickets with catarrhal diarrhoea, chronic pancreatitis, gastro colic fistula, tuberculosis of the lacteals or mesenteric glands, giardiasis (*see* p 258), irritating intestinal poisoning, such as poisoning with boric acid, sprue (*see* p 337), and megacolon or Hirschsprung's disease.

*Radiographic examination* of the long bones generally shows a decreased density of the bone, i.e. a mild degree of osteoporosis.

*Analysis of the faeces*—Fat forms 50 to 80 per cent. of the dried faeces in the acute stages. In quiescent periods the amount is slightly increased, when the patient is on a fatty or milk diet the proportion rises. The fatty acids and soaps (split fat) account for some 80 per cent. of the total fat. The bulkiness and frothiness of the stool is due to excessive carbohydrate fermentation.

**Treatment**—The general principles of treatment are as follows.

1 A low fat diet, consisting of skimmed milk (commencing with two pints daily), orange juice and green vegetables. Later, lean meat, bread, boiled fish, eggs and jam are permitted. All fats are to be avoided.

2 Vitamin D is given as irradiated ergosterol (radiostol) with ultra violet light.

3 To increase absorption, bile salts are recommended by H. Thursfield, being given in gelatin capsules, containing 1 gram of equal parts of sodium glycocholate and taurocholate. A palatable preparation, known as "Elixir Cholalic," is made by Allen & Hanbury.

4 For the anaemia, iron and yeast preparations (marmite) are indicated.

5 The associated tetany and rickets require special treatment on the usual lines.

**Diet**—The essential features of the diet are (1) that it shall contain the minimum of fat, and (2) that the protein and carbohydrates shall be in a form acceptable to the child's digestive capacities.

Protein is usually well tolerated, but carbohydrate often constitutes a difficulty, and various forms must be tried until one suitable to the individual case is found. In infants, skimmed dried milk, for example, separated Cow and Gate reconstituted with water in the proportion of 1 drachm to each ounce of mixture, forms the basis of the diet. To this may be added protein in the form of casein or plasmon. For older children, meat, in the form of rabbit or chicken's heart, or tripe is included in the diet.

The nutritional integrity of the diet must be ensured by the addition

of carbohydrates, but the form in which this is best tolerated varies greatly with the individual child. Dried cereals (Post-Toasties, Cornflakes, Force, etc.) are useful, and may be served as puddings, made with skimmed dried milk. Ripe bananas are widely used, and chestnut flour is a useful variant.

To supply the necessary vitamins, marmite (B), adexolin or radiostoleum (A and D), csogen (A) or ostelin (D), should be given.

The following is a diet given in a case of coeliac disease in a child aged four years —

Separated Cow & Gate (1 drachm with water to 1 ounce)	20 oz
Dextrin	1 oz
Plasmon biscuits	4 oz
Powdered casein	3 oz
Cheese	3 teaspoonfuls
Butter	1 teaspoonful
Honey	1 teaspoonful
Post Toasties	5 tablespoonfuls
Chestnut flour as pudding	2 tablespoonfuls
Radiostoleum	3 minima t d s

Egg and small quantities of cow's milk are gradually introduced. Later green vegetables, potatoes and carrots are added.

### IDIOPATHIC STEATORRHOEA OF ADULTS

Coeliac disease in adults has only comparatively recently been recognized, and the history of its discovery has already been alluded to. There are many reasons detailed on p. 377, for its differentiation from tropical sprue, though many of the clinical and biochemical features are similar. Interest has been aroused by the frequency of this affection in Denmark and other parts of northern Europe, and there is every reason to believe that many instances of non-tropical sprue, so ably described by Thaysen, are identical with idiopathic steatorrhoea of adults which has been recognized in England. E. J. Wood first described this condition in the United States where it was first thought to be tropical sprue.

On careful enquiry, most cases of adult steatorrhoea can be traced to childhood, and hence adult steatorrhoea is assumed to be identical with coeliac disease of children. This is the conclusion arrived at by Bennett, Hunter and Vaughan in their study of fifteen cases. The same symptoms are present as are seen in coeliac disease in children—dilatation of the colon, tetany, osteomalacia, anaemia, infantilism, steatorrhoea, disturbance of calcium metabolism expressing itself in skeletal changes, osteoporosis and often rickets. Glossitis occurred in five cases. The patients may not actually complain of sore tongue, but the tongue presents the bald and shiny appearance, due to atrophy of the filiform papillae, so frequently associated with anaemia. In contrast to the almost constant occurrence of sore tongue in tropical sprue, this symptom is only occasional, though it must be noted that

E H Thaysen described various degrees of glossitis in the majority of his "non tropical sprue" cases

Gastric analysis revealed complete achlorhydria with no total acidity in only two out of twelve cases examined. Abdominal distension was a conspicuous feature in some cases, but was not present in every instance. Where there is extreme meteorism there may be some difficulty in differentiating the disease from tuberculous peritonitis. In six out of eight cases a marked dilatation of the colon was detected by X ray examination, and in two it was pronounced enough to be designated megacolon. There appears to be a definite relationship between the diarrhoea and dilatation of the colon—the greater the colonic dilatation the less the tendency to diarrhoea—and it may be that the dilatation is a defensive mechanism to check the diarrhoea.

The character of the stools is the same as has already been described under coeliac disease in children. In spite of the frequent absence of diarrhoea, steatorrhoea was present in every case. The total fat varied from 47–71 per cent. of all the stools analysed. Tetany was present in fourteen cases and skin lesions in seven, usually in the form of an eczematous or pustular dermatitis. Clubbing of the fingers was found in nine cases and brittleness and ridging of the nails, loss of hair and defects in the enamel of the teeth giving rise to transverse ridges, have been noted. Slit lamp examination of the lens revealed small, flaky, powdery opacities in various layers of the lens. In all these cases the serum calcium was low, as in postoperative tetany.

Bone changes in idiopathic steatorrhoea of adults were first noted by Holst (1927), while E H Thaysen in 1932 emphasized the occurrence of bone pains in the neighbourhood of the great joints in "non tropical sprue". It is clear that there was osteoporosis in his cases for he comments upon the diminished height and the laborious cautious gait comparable to the hunger osteomalacia seen during the 1914–18 War. In Bennett and Hunter's series no normal skeleton was encountered. Ten cases were dwarfed, but the infantilism of stature was not necessarily associated with mental or sexual infantilism. In twelve cases, whether dwarfism was present or not, the bones were in some way deformed. Osteoporosis of varying degrees was seen in twelve cases. It has been noted, however, that there may be no physical signs of associated hypocalcaemia even with a low blood calcium content.

The blood picture was normal, or showed a hypochromic anaemia, hyperchromic megalocytic anaemia, or erythroblastic anaemia. Changes in the leucocytes are usually slight, but leucopenia is common. Those cases with hyperchromic megalocytic anaemia responded well to treatment with marmite. In many respects metabolism was abnormal. Thus, the blood sugar curves, after glucose administration, were flatter than normal and the blood urea was below the normal figure, and in thirteen cases the serum calcium was low.

Irregular attacks of pyrexia have been noted, associated especially with intestinal disturbances.

H Moore, W R O'Tarrell, J. A. Geraghty, J M Hayden, and M A Moriarty have now described ten cases in Dublin, the youngest patient being nineteen and the oldest sixty-three. In almost every detail they correspond with the accounts already given. Skeletal changes were present in every case, and multiple fractures were present in three, in one there were five fractures, in one seven, and in another nine. Under treatment they all united.

R Kark, A W Souter and J C Hayward (1941) have made the interesting observation that sometimes a hemorrhagic diathesis is noted which is quite distinct from scurvy and which has proved to be hypoprothrombinæmia as a result of vitamin K deficiency, and which was corrected by the administration of this vitamin. The patient suffered from recurrent ecchymoses over the backs of hands, elbows, knees and scapular area.

**Diagnosis.**—Diagnosis is made upon the indications which have already been given. There appears to be no essential point of distinction between the features described by Thaysen and those so ably put forward by T I Bennett, D Hunter and J Vaughan.

Reference must be made to the condition known as "congenital steatorrhœa" which is characterized by the passage of butter-like stools, and has been included by Garrod amongst the inborn errors of metabolism. Cases have been described by R Miller and H Perkins (1923) and Spriggs and Leigh during recent years. It is not associated with infantilism or bony changes, and therefore has no relationship to idiopathic steatorrhœa.

The differential diagnosis has to be made from sprue and other forms of steatorrhœa. The differentiation on clinical grounds of idiopathic steatorrhœa from sprue does not appear to offer any particular difficulty to those who have had an intimate acquaintance with the clinical characteristics of sprue. In the first place the tongue and mouth are not affected to the same degree. The anæmia is not marked and the *blood count does not alter*, however much the general condition deteriorates. The diarrhœa in idiopathic steatorrhœa is unaffected by drugs or by diet, and is progressive. The patients have an anxious, pinched appearance, and in the men the hair is silky and tends to turn grey early, even at thirty years of age (Fig 70). These points are illustrated by a case seen by the author —

A man of fifty-one years of age was referred from Dumfries shire with the provisional diagnosis of sprue on February 25 1937. He had never been in the tropics, but had served in Salonica from 1915 to 1917. He had been ill for two years. The main complaint was sprue-like diarrhœa, with progressive wasting, pains in the bones and cramp in the hands and feet. The main features on examination were extreme emaciation, distended abdomen, ridging and brittleness of nails, and low blood pressure (95/70). Superficial and deep reflexes were either diminished or entirely absent. No lens opacities were noted. A slight degree of osteoporosis was demonstrated in the humeri by X-ray examination, together with a loss of calcium content. The blood



calcium (6.2 mgm per cent) and blood-cholesterol (100 mgm per cent) were low. The blood sugar curve was of the flat type. The faeces contained 44 per cent of fat. The blood-count remained at the figure of 4 600 000 red cells per c mm throughout with a colour index of 1. There were few changes in the red blood corpuscles. Fractional test meal showed complete achlorhydria.

The case was observed in hospital for three months before death. Blood transfusions, injections of calcium gluconate and parathormone (Collip), all kinds of diet etc., were tried but no treatment had any effect in stemming the downhill progress. At autopsy the liver, heart and spleen were found to be small and atrophied. The intestinal walls were thinned and transparent, the bones soft and pliable. No other important features were noted.

**Radiographic appearances** — A considerable amount of attention has recently been paid to the radiographical appearances produced by the very evident upset in the normal intestinal functions in this group of diseases. Some of the descriptions hitherto published are still to be regarded as somewhat problematical and how far they are applicable to tropical sprue is yet uncertain.

J. E. O'Sullivan (1941) summarizes the appearances as follows — J. Kantor's sign (1939) consists of obliteration of the usual markings of the *calculus connexities* (sometimes termed moulage sign) with dilatation and consequent segmentation of the barium into clumps. As elaborated by J. McGrath and his colleagues the moulage sign is better described as resembling a tube into which wax has been poured. H. W. Hotz and W. G. Deucher (1941) claim that the main radiological features consist in narrowing of the ileum alternating with atonicity and spasticity, producing a coarse, wavy mucosal relief and increased motility. The duodenum is dilated and atonic, mucosal relief being absent. The upper jejunal folds are broad and band-shaped with small lateral, circumscribed indentations. These findings have been in the main confirmed by A. V. Snell, J. D. Camp, J. Buckstein (1940) and R. Golden (1941), and T. T. Mackie in America, while the first named has claimed that they are modified by adequate liver therapy.

It is stated that the changes in the small intestine are the result of intestinal hurry and interference with normal mixing of intestinal contents, suggesting that the main aetiological factor lies in an absorption defect of the mucosa. For an instructive study of the radiological appearances of the small intestine in health and disease the reader is referred to a paper by E. Spriggs and O. A. Marxer (1937).

**Treatment.**—The treatment of steatorrhoea in adults follows the same lines as that adopted for children, the chief points being control of the steatorrhoea by a low fat diet, control of the carbohydrate dyspepsia by regulation of the intake of starch, relief of tetany by increasing the intake of calcium and of vitamin D, alleviation of the pain and relief of bone deformities, and finally the treatment of the anaemia by increasing the intake of iron or by giving marmite or liver.

Patients can seldom be given as much fat as is present in normal diet without suffering from diarrhoea. A diet of high calcium content should in all cases be supplemented by the administration of calcium lactate in doses of 10 grains three times daily. In cases with tetany injections of calcium gluconate (10 c.c.) are indicated. Vitamin D should be given in every case in which there are clinical or radiographic signs of rickets, osteomalacia, or osteoporosis. It often relieves the bone pains, but any relapse of diarrhoea is apt to interfere with its good effects. It is best given in the form of radiostol tablets (B D H). In



Fig 70 —Idiopathic steatorrhea facies and tongue of the case described in the text

treating all the forms of anaemia it is necessary to remember the importance of adequate dosage. Injections of Campolon or Hepatex should be given in 6 c.c. doses daily. Iron and marmite should be given according to the type of anaemia present.

On the whole, idiopathic steatorrhea of adults is more disappointing to treat than is coeliac disease in children or tropical sprue in adults. It is apparent so far that though nicotinic acid in large amounts does appear to exert some action in controlling the diarrhoea and altering the character of the stools, it has by no means the same curative effect as in tropical sprue (see p. 392).

## PANCREATOGENOUS STEATORRHOEA

**PANCREATIC INSUFFICIENCY**—The normal pancreatic juice contains trypsinogen the zymogen of trypsin (protein ferment) lipase or steapsin (fat ferment) and diastase or amylase (starch ferment)

The considerations upon which a diagnosis of pancreatic insufficiency may be based are as follows—

1 **Internal secretion**—The efficiency of the internal secretion is tested by means of Loewe's adrenalin mydriatic reaction which consists of placing two drops of 1/1000 adrenalin solution on the conjunctiva and repeating in 15 minutes. If the pupil dilates it suggests a deficiency of the pancreatic secretion

2 **External secretion**—The most definite results of failure of this secretion are (1) steatorrhœa (excessive excretion of fat) (2) azotorrhœa (excessive excretion of protein) and (3) increase of diastase in the urine

*Steatorrhœa* or pancreatic stools results from a deficiency of pancreatic ferments. The stools are bulky, frothy and light coloured with an offensive cheesy odour mainly due to excess of fat. The chemical alterations in the stools are mainly due to the excess of fat which amounts to 50–80 per cent of the total weight and consists mainly of neutral fat which cannot be absorbed. The reaction of the stools is alkaline. Comparison should be made with stools of sprue, cœliac disease and idiopathic steatorrhœa which are acid and the excess of fat is due to fatty acids and soaps.

If the pancreatic secretion is defective the stools show a large amount of undigested fat represented by an abnormal percentage of neutral fat. On the other hand if bile is deficient the large amount of undigested food is composed of an abnormal percentage of split fat.

*Azotorrhœa*—The amount of protein recoverable from the stools in pancreatic disease is 30 to 40 per cent whereas from normal fœces it is about 5 per cent.

It is not practicable in a work of this description to give a detailed account of all the pathological conditions of the pancreas which may produce diarrhœa and pancreatic stools but the following is an outline.

In *chronic interstitial pancreatitis* the outstanding features are a gross increase in the interstitial fibrous tissue. The condition known as *hæmochromatosis* is usually associated with advanced pancreatic sclerosis. *Pancreatic cysts* are usually retention cysts being associated with a sclerosing pancreatitis or with calculi. The most common form appears to be the result of irregular necrosis and autolysis. *Pancreatic calculi* are of little practical importance except when impaction occurs with either acute necrosis or sclerosis of the pancreatic tissues.

**Acute necrosis of the pancreas**—This is due to impaction of a gall stone or pancreatic stone in the ampulla of Vater or it may

result from spasm of the sphincter of Oddi. The regurgitation of bile which is essential for the activation of trypsinogen is thus prevented so that auto digestion of the tissues occurs, and the escape of lipase causes *fat necrosis* of the omentum and surrounding tissues.

**Acute pancreatitis** occurs most frequently in obese individuals of middle age, especially males. The condition usually arises as a sequel of infections such as influenza, typhoid, or mumps. A history of gall stones is frequently obtained. In alcoholic subjects, who are liable to attacks of gastro duodenitis, the inflammation may spread to the pancreas through the pancreatic ducts.

The most obvious symptom is progressive wasting with intense indigestion. As a rule gastro intestinal symptoms are indefinite and various. Everything from vague slight distress to severe indigestion with nausea is encountered. Either diarrhoea or constipation may manifest itself. There is usually severe and agonizing epigastric pain, which is thought to be due to irritation of the celiac plexus.

**Chronic pancreatitis**—Chronic pancreatitis may arise from inflammation within the ducts and may be due to pancreatic calculi, to gall stones in the ampulla, or to spread to the pancreas of inflammation of the bile ducts caused by gall stones. A history of biliary colic and gall stones is present in 50 per cent of cases. The symptoms are usually indefinite, and consist of recurrent attacks of pain in the epigastrium, rigors, fever, sweats, vomiting, and diarrhoea, very often accompanied by bulky pale stools. The symptoms may simulate gall stones, so that jaundice is a frequent accompaniment. Glycosuria and diabetic symptoms are rare.

**Stools**—The peculiar pale bulky motions encountered in chronic pancreatitis are especially noticeable when the gall bladder is involved. It is important to note that much of the unsplitted fat, to which reference has already been made, is decomposed by the action of intestinal bacteria in the lower part of the gut. Special attention should be directed towards the microscopical appearances (Figs 71-74).

In **carcinoma of the pancreas** the pain is exceptionally severe, and it is obvious that the irritation of such a sensitive structure as the solar plexus will produce vomiting and other gastro intestinal symptoms. Intense jaundice and glycosuria are usually present in the growths of the head of the pancreas.



Fig. 71—Tropical sprue in acute stage, to show fat globules and fatty-acid crystals.



Fig. 72—Pancreatitis, showing fatty acid crystals, fat globules and undigested starch granules.

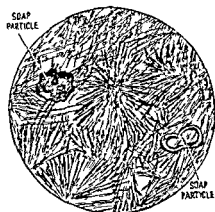


Fig. 73—Biliary cirrhosis, showing sheaves of large fatty acid crystals.

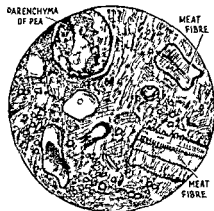


Fig. 74—Fatty faeces of biliary obstruction, showing undigested meat-fibre.

P. H. M. B.

Figs.—71 74—Microscopic appearances of the faeces in the steatorrheas.

## Affections of the Colon Resembling Dysentery

## CHAPTER XXIII

### MUCOUS COLITIS

**Synonyms** —Muco-membranous Colitis    Membranous Colitis  
Irritable Colon    Spastic Colitis    Mucous Colopathy

**Definition** —The term mucous colitis is a convenient one employed to designate a state or dysfunction rather than a pathological condition. The chief feature is the presence of an excess of mucus in the stools attended by various nervous phenomena which may be the cause or the result of the disease. Mucus is a glycoprotein, a normal secretion both of the stomach and of the intestine and is able to take up large quantities of water and dissolved substances. The normal mucus fulfils the functions of softener, lubricant and protective and its production is much increased in infective processes. W. N. Boldyreff suggests that excess of mucus is harmful to the digestion. A. F. Hurst considers that the mucus in the stool has been secreted as a response to irritation caused for instance by the faeces which when they collect in the pelvic colon are often hard and dry.

**Ætiology** —A great deal has been written upon the genesis and treatment of this affection but no discovery of first class importance has been made which sheds definite light on the subject.

In the first place the diagnosis of mucous colitis must be made by a process of exclusion. A. F. Hurst insists that this diagnosis should never be made until investigation has shown inflammation of the colon to be present. Although the term irritable colon which is often employed implies that the musculo neural apparatus has lost its powers of co ordination and correlation probably the fact is that this condition actually precedes the development of mucous colitis. The excessive secretion of mucus is usually associated with spastic contraction of the colon or spastic colon.

W. A. Bastedo and others who have written about this malady agree that there is much difference of opinion about its character and no agreement about its ætiology.

*The following theories have been put forward* 1 That the condition is purely neurogenic and that the mucus produced in the bowel is a hypersecretion. 2 That the condition is catarrhal the result of inflammation of the mucous membrane of the colon. 3 That the condition is in part neurogenic and in part inflammatory. 4 That the condition is in part or wholly due to hypersensitivity to the normal bacterial inhabitants of the intestinal canal. 5 That it is an intestinal manifestation of an allergic disease.

*The allergic factor*—Allergy is defined as a condition of altered reaction on the part of tissue cells to foreign chemical agents. Familiar allergic conditions are asthma, migraine, eczema, urticaria, hay fever and angio neurotic oedema.

The allergic condition produces enterospasm, a condition of the bowel in which strong painful contraction of the longitudinal and circular muscle fibres takes place. Various authorities have reported cases where abdominal pain is due to hypersensitiveness to certain foods. The explanation of this type of allergy is difficult to find, but it may lie in the inheritance of a constitution which is hypersensitive to foreign proteins. Mechanical factors must also be taken into consideration as the mucous membrane of the bowel is very irritable when the bowel is in a sensitive state. (A. A. Bissett.)

D. C. Hare studied thirty-eight cases of mucous colitis, all in women and divided them into four groups according to their allergic histories. She found nineteen strongly positive with a personal history of asthma, migraine, rhinorrhoea or hay fever, and eleven weakly positive with personal history of simple or slight allergic attacks with or without a positive family history.

Allergic disorders tend to be intermittent or remittent, and the actual attacks to become more severe and more frequent. Physiological states exert, as a rule, a definite influence on the course of allergic diseases. Menstruation, for example, is generally recognized as likely to produce exacerbations (this is certainly the case in mucous colitis); pregnancy, on the other hand, gives comparative freedom from attacks.

Hare has also drawn attention to the frequent close relationship between the first onset of colitis and such infections of the upper respiratory tract as influenza, acute catarrh and tonsillitis. The allergic response of sensitized tissues is characterized by increased permeability of the capillaries, oedema of the mucous membranes and spasm of unstriated muscles; it may be limited to the colon. It is pointed out that one of the functions of the colon is excretion, and it may be that bacterial products expose the tissues to special damage or sensitization.

*Neurogenic factor*—At present the majority of investigators incline to the hypothesis that mucous colitis is mainly neurogenic, this view has the support of J. L. Lichty, E. D. Kiefer, T. R. Brown and J. A. Bargen. Other interpretations have been put forward by J. E. McLoone (1931) and others; they consider that mucous colitis is correlated with the mode of living and eating of the present generation, with the rush and hurry of the daily routine and the lack of regular meals, proper food and daily bowel evacuations. It is the mode of life of the individual in conjunction with an unstable nervous system that produces the irritable bowel and this condition once established the vicious circle is complete. Sufferers from mucous colitis are usually what is known as "colon minded".

The more this subject is studied, the more emphasis is laid upon the



essential rôle of the nervous system in governing both the motor functions of the bowel and its secretion of mucus. It is not easy to determine whether abnormalities of mucus secretion and of bowel action cause the symptoms, or whether symptoms and abnormalities of mucus secretion are alike the result of disorder elsewhere in the body. F. H. Kruse has devoted attention to the innervation of the intestinal tract in his search for an explanation of spastic colitis, and he considers that the parasympathetic nervous system, notably the vagus, is the activator, while the sympathetic system with its paravertebral ganglia acts as the inhibitor or depressor. Auerbach's plexus, on the other hand, is chiefly concerned with the act of peristalsis, and the sacral plexus with the muscular tonus of the bowel.

E. I. Spriggs, in a scholarly and penetrating analysis of mucous colitis, gives it as his opinion that the two main causes are neurosis and constipation. His experience leads to the view that an unstable nervous system is a predisposing factor. The pronounced form of the condition known as enterospasm is usually found only in those engaged in mental work. The almost constant complaint is constipation, and in his opinion the treatment of real or alleged constipation by irritating aperients is as potent and frequent a cause of colonic disorder as is the constipation itself. He holds, indeed, that constipation is less harmful to the colon than are the irritative aperients.

C. Hunter (1932) considers that the peristaltic action of the colon is normally and automatically regulated by impulses from Auerbach's plexus. The colon itself is, we know, insensitive to cutting, pinching and burning, and it is probable that in the spastic colon there is a tonic hardening with rigidity and narrowing of the lumen of some portion of the colon, a condition which may last for hours and even for days.

That mucous colitis is not strictly a disease of the colon may be inferred from a case reported by W. A. Bastedo in which the colon was removed, yet all the symptoms of mucous colitis, even to colic and spasm with the passage of strings of mucus, persisted.

**Incidence**—It is probable that mucous colitis is more common in women than in men, possibly because of the less stable nature of their nervous systems. In the Mayo Clinic, according to Barger, 58 per cent of the cases were women and 42 per cent men. In 50 cases, J. A. Ryle found 17 males and 33 females, the age limits being nineteen and seventy eight years. A similar condition is recognized in infants and children.

The type of person who develops mucous colitis has often been remarked upon. Ryle speaks of him as a dark eyed, lean and spare individual, probably descended from a nervous stock. Patients may be well nourished, or even obese, but the majority of sufferers are of the lean, highly intelligent and introspective type. It is rare to meet with the condition in the true Scandinavian type, with blue eyes, fair hair, and healthy complexion, and with a placid disposition.

Occupation appears to have a definite bearing on the incidence

Persons leading a sedentary life make up the greater number of patients, whereas agricultural or other labourers, or those following active pursuits, are seldom found among them.

Mucous colitis is a common disease of residents in the tropics, in fact it may be said to be as common among the busy public servants in hot countries as it is among business people (especially those of the Jewish race), stockbrokers and bankers, in temperate countries.

The dysenteries, either of the bacillary or amœbic form, owing to the bowel habits they engender, are very apt to be followed by spasticity of the colon. This is an undoubted factor, added to the nervous stimulus which locates the fulcrum of nervous impulses upon the intestinal canal.

Investigation into the previous histories of genuine cases of mucous colitis in the tropics has shown that, when a person of a certain type of mentality has suffered from some form of dysentery, his mind, having become concentrated upon the functions of his intestines, exerts an undue influence over the bowel and sooner or later mucous colitis develops. The danger of not recognizing the true nature of such cases can readily be appreciated, because consistent treatment for well established dysentery only exacerbates the bowel condition.

In 141 consecutive cases of mucous colitis and spastic colon under the author's care in the Hospital for Tropical Diseases 12 (8.5 per cent) were secondary to intestinal amœbiasis and 24 (17 per cent) were secondary to bacillary dysentery.

The following complications were found associated with the colitis

Definite hyperthyroidism	2	Dental sepsis	3
Hyperchlorhydria,	2	Giardiasis	1
Chronic appendicitis	2	Syphilis (W R ++)	2
Internal hæmorrhoids,	2	Diverticulitis	1
Trichuris trichiura infection	1	Urticaria,	1
Ascariis infection,	1	Septic tonsillitis	1
Gall stones	1		

**Symptoms**—Although the symptoms of mucous colitis resemble those of dysentery, yet in the majority of cases there is constipation rather than diarrhœa. Incessant liquid diarrhœa may on the other hand, be a very real symptom, but it is unaccompanied by the grave emaciation seen in other forms of intestinal disease. In the constipated patient suffering from mucous colitis the stools are fragmented, and the fecal masses are of small calibre, and flattened or ribbon like. When diarrhœa is present it is never severe. It may be distressing to the patient, but usually there are not more than three or four motions in the twenty four hours, and they are passed in a relatively short period.

Mucus is present in the stools in variable quantities at different stages of the illness. When the patient is badly constipated efforts at passing a motion may result in the outpouring of several ounces of gelatinous mucus, which is often passed in ropes or strings, and may

be so dense as to resemble actual mucosa, when it is often mistaken for a membrane

The faeces may be characteristic of the different types of the disease. Where the colon is very irritable there are scybala surrounded by mucus. In catarrhal mucous colitis the mucus is very much increased in quantity, and the typical motions are semi solid, mixed with mucus derived from the upper colon. This is often described as diarrhoea. In membranous colitis, large casts may appear as rolled up membrane which can be recognized when it is floated out in water. There is usually bleeding both before and after passage of this membrane.

Sometimes the mucus is passed intermittently, when the stools come to resemble some badly made meat jelly or under cooked vegetable marrow. The amount of mucus passed per day is very variable—it is said that as much as 1 000 c.c. may escape. In colour it is grey, greyish white, or brown. The passage of mucus in the stools is very disturbing to most patients, but this is due not so much to any associated distressing symptoms but rather to the fact that the patient's attention has been directed to the presence of this abnormality.

The abdominal pains vary greatly in severity and in their situation. There is discomfort in the lower abdomen, often with actual pain—a dull continuous ache rather like that of chronic toothache which may occasionally be so intense as to necessitate the administration of morphia. There may be languor, gaseous dyspepsia, eructations, and periods of nausea and vomiting which may immediately follow the taking of food. There is usually epigastric distress accompanied by much rumbling and gurgling in the abdomen which often attracts the patient's attention to his stomach as the cause of his intestinal disorder. That there may be more or less acute pain in mucous colitis must be duly appreciated, for there is a danger of the clinician confusing the pains with those of ulcer, gastric intestinal or duodenal. Ryle in England and Lick in Germany have repeatedly emphasized that a spastic colon is a common cause of persisting and recurring pain in the right iliac fossa, and that it may, therefore, closely simulate appendicitis.

There are also various nervous disorders associated with this condition—nervous exhaustion, mental depression, lack of concentration, persistent headache, paraesthesia, syncope, and vertigo. Dead and numbed fingers are a common complaint and, like other subjective symptoms, are apt to be aggravated by cold and fatigue.

The abdomen usually appears normal on inspection, distension being noted in a small proportion of cases. In spastic colitis, the bowel can usually be palpated and is tender on deep pressure, especially in the left iliac fossa. Occasionally, the ascending and transverse colons may be felt as a hard cord.

In most cases of mucous colitis and spastic colon, there is hyperacidity, Van Noorden found it in 70–80 per cent of his cases. The experiments of other workers (C. Hunter, 1932) support this contention.

Smith Paul and Fowler found that the experimental introduction of 500 c c of air into the colon by means of a rubber bulb and rectal tube was followed at once by a striking increase in tone of the pyloric end of the stomach

In its most intense form this colitis is accompanied by the passage of membrane and casts of the large intestine and is then by some authorities designated as membranous colitis. Since however in these cases accumulations of mucus which closely simulate a membranous cast are quite commonly extruded from time to time the term *mucos membranous colitis* is more accurate. Such severe cases are by no means common and when they do occur are distinctly more distressing and more difficult to treat than are cases of the ordinary mucous colitis.

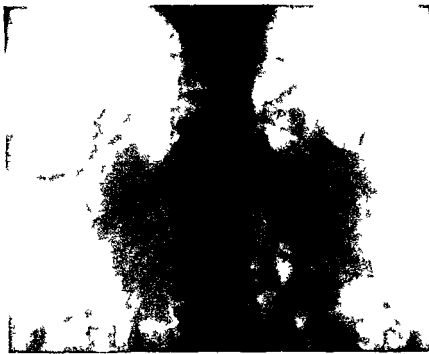
There are few descriptions of this mucos membranous colitis in the literature. The patients are usually young adults, the majority being women and are of a highly sensitive introspective type. From time to time they suffer from attacks of severe intestinal pain and colicky spasm accompanied by the passage of a cast of the mucous membrane of the large intestine, usually this is only a few inches in length but casts from one to two feet long have been recorded. The casts which are usually preceded and followed by a show of blood, are passed at the end of defecation. Following upon their passage, the patient continues to pass blood stained mucus for a few days. Except for the periodic exfoliation of membrane, these patients resemble ordinary cases of mucous colitis but they usually experience much more pain and a feeling of rawness or soreness of the large intestine.

There is no reason to believe that the condition of mucos membranous colitis is grafted upon any previous specific infection of the mucosa.

In 1931 a woman aged twenty nine years came from Malaya where she had contracted amoebic dysentery in 1928. Subsequently she had suffered from recurrent attacks of diarrhoea in which much mucus and often casts of the mucosa were passed. On admission to hospital she appeared toxic and ill with persistent pyrexia of 100-101° F. The tongue was dry and fissured the abdomen sunken and tender. The faeces contained eggs of *Ascaris* and *Trichuris*.

On several occasions when in hospital she was attacked by bouts of abdominal pain during which she became nauseated and faint and when the colic had subsided, membranous casts of the mucosa appeared in the faeces. On one occasion such a tubular cast of the sigmoid colon measured 11 inches. When viewed through the microscope the cellular elements in its composition could be recognized. After the passage of the membrane the patient was exhausted but pain and distress were relieved. A loss of weight of 7 lb was noted. Although the diarrhoea persisted yet there was singularly little blood in the faeces. Ridding the bowel of the helminthic infections did not unfortunately benefit the general condition. This was the most distressing case of mucos-membranous colitis the author has yet encountered.

The author has notes of four other cases all in women in which blood and mucus with shreds of mucous membrane were discovered in the faeces. The



*Photo D. G. Tatham, Cordner*

Radiograph of liver showing gas in liver abscess cavity after aspiration (*Dr V H Fairley's case*)

## AMŒBIC ABSCESS OF LIVER

PLATE XIII



*Photo Dr. Bertram Sares*

Radiograph of barium enema in mucous colitis,  
showing characteristic spasm of descending colon  
and sigmoid

**MUCOUS COLITIS**

**PLATE XIV**

patients ranged in age between thirty and fifty three. One came from India, where she had been tentatively treated for bacillary dysentery, one from Egypt, where she had been regarded as suffering from amœbic dysentery, and one from Buenos Ayres. The chief complaint in this last instance was a constant gnawing pain in the left side of the abdomen accompanied by constipation, the passage of membrane appeared to be the direct result of excessive purging with Epsom salts. The fourth case was that of a woman, thirty years of age, who had never been abroad, but who had suffered from mucous colitis for seven years. The exacerbations of the bowel complaint coincided with attacks of *Bacillus coli* pyelitis.

*Mucous colitis in children*—That mucous colitis is not peculiar to any period of life is shown by the fact that a somewhat similar condition is recognized in infants. It is generally considered that at this age it is a reflex condition brought about by fat intolerance which causes a catarrhal state of the bowel. Mucous colitis is seen in the eczematous type of child, in whom the passage of stools containing mucus may alternate with bouts of eczema.

The most typical picture is seen in older children, those of two to seven years of age. In them the attack commences with a bout of fever, very often with tonsillitis, and the stools are very loose and offensive, and contain large quantities of mucus. Examination of the urine usually shows the presence of acetone. These attacks last two or three days, occasionally a week, and then subside.

Children who suffer from mucous colitis are of a thin, nervous type—the type usually subject to cyclical vomiting, with a low fat tolerance, and a tendency to form acetone.

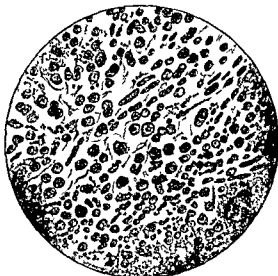
*Diagnosis*—The diagnosis of mucous colitis can only be arrived at on general grounds. As no infallible scientific test is available reliance must be placed on the history of the case and the general train of symptoms, the physical condition of the patient and his mental attitude being taken into account.

The value of following out a definite programme in the investigation of intestinal dysfunction cannot be over-emphasized. The patient should leave the consulting room with a feeling that he has been through the most thorough examination which can be made, and he should be encouraged to disclose all relevant information.

*Radioscopy*—The barium enema method is useful mainly in excluding organic disease of the large intestine. Local spasm of the bowel is well brought out, and is usually observed in the region of the sigmoid colon. J. A. Barger writes that the "string sign" of Crane which consists of a thin line in the radiogram along the course of the colon (probably caused by barium adhering to the mucus in the bowel), has been presumed to be indicative of mucous colitis. In a large series in the Mayo Clinic however, he was unable to establish it solely as pathognomonic of colonic disturbance. C. Hunter considers that X-ray appearances support the view that in spastic colitis there is a tonic hardening of some portion of the colon, but issues a warning

that mucous colitis should never be diagnosed from X ray findings alone (Plate XIV)

*Examination of feces*—The stools may consist of hard scybalous masses coated with whitish strings of mucus or they may be semi formed and gelatinous owing to the liberal admixture of mucus derived from the bowel wall. Where there has been exfoliation of the mucosa as in muco membranous colitis, a cast of the mucous membrane of the whole tube or of small portions of it is recognizable. It is necessary to emphasize that this membrane is not passed with every motion but only during the periodic exacerbations which occur in this form



P H V. B

Fig 75—Appearance of mucus secreting cells in the exudate in mucous colitis

The author believes that considerable help may be obtained from a microscopic examination of the feces. The cellular exudate in mucous colitis consists mainly of mucous cells and remains of goblet cells, which may be recognized amidst the glairy mucus (Fig 75). Very often columnar intestinal cells are also visible as well as squamous cells derived from the anal margin. A F Hurst has emphasized that the mucus never contains leucocytes or red blood corpuscles.

Intestinal sand was found by W Hale White in 10 per cent of his cases. It occurs intermittently, and as much as a tablespoonful may be passed in a day. It consists mostly of calcium phosphate with traces of oxalate and of magnesium, iron and silica.

Bacteriological culture of the feces is distinctly misleading. A variety of intestinal coliform organisms can usually be isolated and



very often hæmolytic streptococci also but they appear to be of no diagnostic significance

*Sigmoidoscopy* is helpful in forming a diagnosis, the author considers it indispensable. The mucous membrane is generally pale with a definite yellowish tinge, and is covered—in some cases almost plastered—with sticky, adherent mucus. In the upper part of the rectum and lower sigmoid this mucus can often be observed being propelled by peristaltic action (Plate XIX, A, facing p 450)

Sigmoidoscopy in these cases is usually distinctly painful, as the introduction of the instrument causes a reflex contraction of the bowel. On account of this spasm, considerable difficulty may be experienced in introducing the sigmoidoscope.

*Differential diagnosis*—Every form of dysenteric disorder enters pertinently into the diagnostic picture inasmuch as differentiation has to be made from every other intestinal condition to which it may bear even a superficial resemblance. Among these may be mentioned chronic appendicitis, duodenal ulcer, carcinoma of the colon, even intestinal obstruction, renal colic, and, in women, ovarian or tubal disease. In addition, it is in both sexes often associated with the neurasthenic state and hypochondriasis.

In many cases the pain experienced is of that degree of severity to be expected in acute inflammatory conditions of the bowel, in others though of course it may be less severe, it is none the less chronic. It is, therefore, hardly to be wondered at that the patient's mind dwells with anxiety upon the significance of the symptoms. J A Ryle has pointed out that most of these patients live in constant dread of some severe organic disease of the intestines.

*Treatment*.—The treatment of mucous colitis and spastic colon is by no means easy. It should be so planned as to minimize the fears the patient entertains regarding himself, and to foster a sense of confidence in the ability of his medical attendant to cure him. The first thing to do is to try the effect of a psychotherapeutic approach—to convince him that, however serious the signs and symptoms may appear, they are not an indication of a severe or incurable malady. Indeed, the mortality from mucous membranous colitis may be set down as nil.

Great care should be taken regarding the previous history of the patient, especially the circumstances under which the disorder arose.

Attention should be directed towards (a) the nervous instability, (b) the general health, and (c) the functions of the colon. As regards the first it is essential that bodily rest and full nights' sleep should be obtained. To ensure this, various sedatives, e.g., bromide mixtures, can be administered. A very satisfactory compound is Euvalerol B (Allen and Hanbury), which contains phenolbarbitone (sodium luminal) together with bromide and valerian. Two drachms of this are given in water three times daily. Improvement in general health is best attained by regulating the diet and by correcting the constipation.

This calls for lubricants such as liquid paraffin (1-2 drachms) or Petrolagar. Whether constipation is actually a fact can be established by a barium meal.

*Treatment to re establish the function of the colon*—For the pain of colonic spasm, there is nothing more useful than a mixture of bromide and belladonna such as the following—

R. Tinct bellad	5 min
Sod brom	5 gr
Aq chlorof ad	$\frac{1}{2}$ oz

Half an ounce to be taken morning and evening

The addition of tincture of hyoscyamus to this mixture may be of distinct value

Stacey Wilson and others have advocated the following mixtures—

R. Liq ferr perchlor	15 min
Liq hydrarg perchlor	15 min
Tinct hyoscy	15 min
Syr aurant	60 min
Aq chlorof ad	$\frac{1}{2}$ oz

Half an ounce with water three times daily ten minutes before meals

R. Bism salicyl	15 gr
Salol	10 gr

To be made into a powder

or R. Bism salicyl	5 gr
Salol	5 gr
Calomel	$\frac{1}{4}$ gr

In tablet form To be taken three times daily before food with a small quantity of water

For acute attacks of colonic spasm there is nothing so efficacious as full doses of atropine sulphate (1/50-1/100 grain) given by injection, and sometimes adrenalin 1:1000 (5-10 minims) by hypodermic injection is useful.

For soothing the bowel the author has found Iso gel (Allen and Hanbury) in large doses very conducive to the patient's general comfort. His practice is to give 1 drachm (1 teaspoonful) three times daily together with 1 drachm of a kaolin preparation Kaldrox (Petrolagar Laboratories Ltd). All authorities are agreed that irrigation of the bowel by high colonic lavage and the injection of large quantities of fluids far from relieving the condition tend to increase the secretion of mucus by unnecessarily irritating the mucosa. J G Mateer and J I Baltz recommend sodium ricinoleate in 5 gram enteric-coated soricin tablets three times daily before meals given over a long period. The routine dose should be six tablets a day. Moderate injections of a bland substance such as warmed olive oil (5-10 ounces injected slowly) act as a soothing agent and a mild aperient. The routine treatment with bismuth subgallate 5 per cent suspended in

10 ounces of olive oil and used as a retention enema, has also been found to be of great benefit. Cod liver oil emulsion—in the proportion of 1 part to 4 parts of water (as retention enema)—is agreeable and very soothing. Eight ounces should be injected.

As emphasized by Barger, *occupational therapy* plays a great part in the treatment of this colitis. A patient must try to cultivate a suitable frame of mind in order to get the best out of his treatment, and should be encouraged to engage in some constructive, interesting, and time consuming activity. Great things often can be accomplished by the simple expedient of keeping the hands busy.

*Diet*—It is probable that diet does not play a very great part in the treatment of mucous colitis so that authorities differ greatly in their opinions on this subject. The diet should be generous, varied, and well balanced, free from irritating ingredients such as tough meat and vegetable fibres. Milk in large quantities does not usually agree. Eggs in scrambled form, in omelettes, or in custard with junket, plain and cream soups and well cooked milk puddings are permitted.

*Fish and meat*—Fish is to be recommended—boiled, steamed, or baked, but not fried, also chicken or game, whether roast or baked, tripe, well cooked sweetbreads, and roast mutton and beef.

*Vegetables*—Mashed potatoes, cauliflower puree, brussel sprouts, cabbage, carrots, turnips, and boiled tomatoes are suitable.

*Fruit* should be well cooked and passed through a sieve. Apricot fool, apple meringue, and black currant fool are suitable.

*Other food*—White bread in thin slices, or any smooth plain biscuits may be allowed.

*Drinks*—Mucous colitis patients should drink sparingly at meals, but plenty of water should be drunk between them. Freshly made weak tea, or coffee with milk, and light wine are best.

Food should be taken regularly. Frequent small feeds are recommended.

*The treatment of mucous colitis in children*—Children with acute mucous colitis should be given no solid food. All milk should be stopped, and glucose water or orange juice and water substituted. When the desire for food has returned, one of the dried milks such as skimmed Cow and Gate, Glaxo, or Horlick's, should be commenced. As stools improve, the child should be encouraged to take more solid diet, such as junket, custard, milk puddings, etc.

Medicines are not of great value for children. Bismuth oxy carbonate and Kaylene in large doses,  $\frac{1}{2}$ –1 drachm, should be given three to four times daily, and the following is a very useful mixture—

R. Pulv. rhei	2 gr
Pulv. jalap	2 gr
Pulv. scammon	2 gr

To be given three times daily

*Prognosis*—In the minor forms of mucous colitis, the outlook is good if the underlying cause of the malady can be dealt with. If it

is constipation, or the unregulated use of aperients, then the remedy is easy. The neurasthenic symptoms may also be mitigated when the patient has succeeded in regaining confidence in himself. Those cases with colospasm or painful spastic colitis do very well after a prolonged holiday and relief from mental strain. It must be remembered both by the patient and his medical adviser that the condition is not inherently serious, and is never fatal. At its worst it is an inconvenience.

Prognosis is naturally better when the case is taken in hand early, and is seriously and energetically treated. The subject of intestinal neurasthenia with recurrent membranous crises is a particularly difficult patient to deal with. But no cases are so hopeless that all attempts at further treatment can be discarded. However tragic these crises may appear, they do not in any way tend to shorten life.

## CHAPTER XXIV

### IDIOPATHIC ULCERATIVE COLITIS

**Synonyms.**—Colitis Gravis (German), Chronic Ulcerative Colitis, Thrombo Ulcerative Colitis, Ulcerative Recto Colitis Granular Rectitis

**Definition.**—The term "colitis gravis" is in many ways preferable to "ulcerative colitis" as it embodies the main features of this severe disease. The latter is by no means a satisfactory designation, because ulceration of the colon is not invariably present, and, when it is, it usually denotes a fatal termination. The tendency to acute inflammatory exacerbations and to periods of quiescence abruptly terminated by relapses, would entitle it to the designation "non specific inflammatory colitis". Nevertheless, the term "ulcerative colitis" has been so hallowed by long usage that it has attained an international character and is therefore retained. There remains, however, no doubt in the minds of those who have studied the subject that, whatever it is called, it represents a distinct disease.

**History.**—Although this disease is becoming increasingly and indeed alarmingly common at the present time, there are but scant references to it in the history of medicine. A coloured drawing by Cruveilhier (1829-42) depicts the condition, while Wilks and Moxon in 1875 mention it in their lectures on pathological anatomy. Allchin, in 1885, exhibited a typical colon at the Medical Society of London and in 1888 W. Hale-White described the condition well. P. Lockhart Mummery in 1907 emphasized the need for proctoscopic examination in all cases of dysentery, and by this method did much to bring about the recognition of colitis gravis as a distinct disease.

**Ætiology.** *Bacillary dysentery theory*—That this grave colitis may be in some way related to bacillary dysentery or caused by one of the organisms of the dysentery group has been urged by many writers, but modern opinion inclines to the view that the occasional discovery of dysentery like bacilli in cases of ulcerative colitis does not necessarily postulate ætiological relationship. A. F. Hurst has, since 1921, been an ardent advocate of the relationship of ulcerative colitis to bacillary dysentery, basing his views upon the somewhat similar pathological processes and the response of some of his cases to treatment by anti-dysentery serum. This view has also been urged by Leusden, Einhorn, Thorlakson, and Cadman. In 1912, Nabarro isolated the dysentery bacillus at the autopsy on a child in Great Ormond Street Hospital, London, and since then he has found that this bacillus is responsible

for cases of chronic colitis in small children. It is not, however, by any means proved that these cases correspond to cases of ulcerative colitis in adults. Recently A. I. Hurst and F. A. Knott have returned to the attack, and have brought forward more evidence that ulcerative colitis is a sequel or direct result of infection of the large intestine with one of the recognized dysentery organisms, or one of its allied forms. Investigations of the faeces of fifty-four consecutive cases of ulcerative colitis were made with the result that *B. dysenteriae* Flexner was isolated in three and *B. dysenteriae* Sonne in one. The significance of the organisms isolated from the remaining cases was doubtful. The majority of cases in Great Britain are Flexner infections, and these workers consider that ulcerative colitis is a direct sequel of a previous dysenteric infection of which the organisms and the agglutinins they evoked in the blood have disappeared.

D. Kling has consistently regarded ulcerative colitis as being of the same aetiology as chronic bacillary dysentery. A. Winkelstein and C. Herschberger (1935), in investigating the bacteriology of sixty cases in the United States, isolated strains of dysentery bacilli in seven. They further examined the stools for the presence of anti-dysentery bacteriophage, and claim that they were able to demonstrate such an active substance in 36 per cent. Intradermal tests with dysentery toxins gave approximately the same percentage as did normal controls.

T. T. Mackie (1932) considers that the lesions of chronic bacillary dysentery differ in no material respect from those encountered in many cases of ulcerative colitis, and he confirmed this by isolating dysentery bacilli from 20.4 per cent. of a series of cases. On the other hand, J. A. Barger, M. C. Copeland and L. A. Bure (1931) reported that in their large series of cases they had been unable up to that date to find any previous dysenteric infection.

*Mucous colitis theory*.—There are many who think that ulcerative colitis may be the ultimate result of a catarrhal state of the mucosa, or what is known as mucous colitis. The disease is frequently found to commence with an outpouring of mucus from the bowel, and gradually to progress to the ulcerative stage. Thus does not, however, by any means prove that the two conditions are identical.

E. I. Spriggs (1934) holds that what he terms chronic mucous colitis may progress to infective catarrhal colitis. He believes that ulcerative colitis occurs in those who are unhealthy from some other cause—who have, for instance, rectal disease. In one-half of his cases rectal disease had preceded the ulcerative colitis, but then, in half it had not.

*Barger's diplococcus theory*.—J. A. Barger has, since 1930, reiterated his belief in the specificity of a diplostreptococcus found in the faeces and in the intestinal lesions. This organism has been isolated from periapical dental abscesses in 149 patients with chronic ulcerative colitis and has also been found in the tonsils of 100 ulcerative colitis patients. T. J. Cook obtained cultures of the diplostreptococcus from



1, Acute hæmorrhagic colitis, 24 hours after prostatectomy, resembling acute bacillary dysentery (*From London Hospital*)



P H M B

2, Acute ulcerative colitis of ascending colon (*From Hospital for Tropical Diseases*)



3, Subacute ulcerative colitis of sigmoid colon, showing great induration (*From Hospital for Tropical Diseases*)



P H M B

4, Chronic ulcerative colitis with gross destruction of mucosa (*From Hospital for Tropical Diseases*)

## PATHOLOGY OF ULCERATIVE COLITIS

### PLATE XV



*Photo Dr G. Maher Connors*

Radiograph of large intestine (negative), demonstrating regional ulcerative colitis affecting transverse and descending colons (Dr N. H. Fauley's case)

## ULCERATIVE COLITIS

PLATE XVI



peri apical abscesses of fifteen patients suffering from the disease. He filled the pulp cavity of the teeth of fifteen dogs with cultures of the organism, and it is said that several of these animals developed chronic ulcerative colitis eight to twelve months after the inoculation.

This organism, usually known as "Bargen's diplococcus," belongs to the green-producing group of streptococci. It has been obtained from approximately 80 per cent of patients with chronic ulcerative colitis who were examined at the Mayo Clinic over a period of several years. Belief in the specificity of this organism is strengthened by the fact that frequently tonsillectomy, removal of infected teeth, or acute infections of the upper respiratory tract cause marked exacerbations.

F. W. Rankin, J. A. Bargen, and L. A. Bine evolved a technique for cultivating material from the bases of ulcers obtained by the proctoscope with sterile cotton swabs. This material was inoculated in tubes of dextrose brain broth. After from four to six hours in the incubator, further subinoculations and preparations were made and stained for diplococci. Eventually the diplococcus was isolated in blood agar and found to ferment dextrose, lactose, saccharose, maltose, raffinose, and salicin.

These facts have convinced Bargen and his collaborators that chronic ulcerative colitis is a disease of bacterial origin and that the primary exciting factor is the diplostreptococcus. Their results have been confirmed (1934) by H. H. de Jong, and others.

G. M. Dack, T. E. Heinz, and L. E. Dragstedt (1935) made a bacteriological study of the contents of the colons of three patients in whom ileostomy had been performed. After the operation there was a marked change in the type of organism predominating in the bowel, and in the course of months the flora became largely anaerobic. The organisms isolated resembled *Bacillus necrophorus*, which has a tendency to produce spreading lesions in rabbits. It is probably present in the normal intestinal tract, since it developed in necrotic membranes formed over areas of rectum denuded of mucosa. Positive agglutination tests were obtained with cultures of this organism in the sera of five ulcerative colitis patients.

*Ultramicroscopic virus theory*—The possibility that ulcerative colitis may be due to a virus of the filterable group, and the pathological picture produced by the passage of such a virus through the intestinal mucosa, has been entertained, but there has been little experimental work to support it. The most convincing is that of F. Gallart Monea and P. D. Sanjuan in 1935. They made a curettage of the mucosa through a proctoscope and, after emulsion in normal saline solution, filtered it through a Chamberland filter, and injected it intravenously into rabbits, guinea pigs, and dogs. In these animals they claim to have reproduced the typical disease, but the results are somewhat vitiated by a statement that a similar virus can be obtained from the mucosa of normal individuals.

E. M. Paulson (1937) suggested that the virus of ulcerative colitis might be related to that of lymphogranuloma. He prepared antigens from colonic exudates of patients with chronic ulcerative colitis and obtained positive intradermal tests with this extract in cases of lymphogranuloma, though negative ones with healthy individuals or patients suffering from other conditions. This had also received support from the work of W. Dick (1934) who first suggested the correlation of these two conditions. However, E. C.

Rodaniche *et al* (1940) have repeated Paulson's work and have concluded that these two diseases are quite separate in their aetiology. The confusion has probably arisen from the somewhat similar symptoms evoked in early cases of lymphogranuloma infections of the rectum.

*Deficiency states*—D. C. Hare concludes that there is evidence in favour of adding this form of colitis to the list of deficiency disorders of the gastro-intestinal tract. A study of experimental vitamin deficiencies shows that both vitamin A and the vitamin B complex are necessary for the development of a healthy mucous membrane in the intestine and for maintaining resistance to infection.

Ulcerative colitis resembles the deficiency state in so far as it occurs in attacks with spontaneous remissions, and relapses without apparent cause. One of the chief functions of the colon in carnivora is to act as an excretory organ, and it exerts a remarkably selective capacity with regard to drugs, being particularly concerned with the excretion of calcium, iron, and bismuth. The special tendency of metabolic toxins to cause colitis, as in uræmia, is probably due to their elimination by this route.

T. T. Mackie and R. E. Pound (1935) claim to have demonstrated a deficiency state, which they consider plays a part in the aetiology, in 62.8 per cent of chronic cases. They found indications of it in the buccal and lingual mucosa, the skin, the type of anaemia present, and the blood chemistry, and they hold that in advanced cases the lower portions of the small intestine are also involved.

*Predisposing factors*—In this connexion T. A. Bergen and J. W. Kemble (1935) specially investigated twenty patients. In no instance was another member of the same family affected, nor did the previous history of the sufferer yield any positive information. The psychological element as a predisposing factor has been stressed by M. Paulson (1932).

R. Bensaude, P. Oury, and H. Danz consider that ulcerative colitis, by reason of its sporadic distribution, its questionable evolution, and its bad prognosis, is a definite clinical entity, but they do not believe in its bacterial nature, and put forward the idea that there is an allergic state of the mucosa in this disease.

A. H. Logan published a statistical study of 117 cases, which is the largest series reported up to date. He believes that the basic factor is some metabolic disturbance.

*Summary*—This review of the various opinions held concerning the fundamental aetiology of ulcerative colitis makes it hardly necessary to point out that knowledge on this important subject is still in an unsatisfactory state. Not one of the theories so far advanced is consistent with all of the many curious aspects of this disease. The author himself favours the view that ulcerative colitis is due to the excretion of toxins through the intestinal mucosa, resembling in this respect the acute colitis of præmia and the acute hæmorrhagic colitis of mercury poisoning. Similar views have been expressed by J. A. Ryle. This opinion receives support from a study of the pathology of the disease, and from its sporadic occurrence among patients of a certain type and of a particular age.

*Pathology*.—According to most authorities, including C. Duke, ulcerative colitis begins as an acute inflammation of the mucous

membrane of the colon; this leads to necrosis, which may be partial or widespread, and is followed by the separation of sloughs and by superficial ulceration. Should the ulcers heal up, ragged polypoid tags of mucous membrane remain in 10 per cent of cases. These are not true adenomatous proliferations. Strictures of the colon proximal to the hepatic flexure are often present. It is a curious point that, in spite of the intestinal ulceration, urinary infections are no more common than they are among the general population.

B Vimtrup states that the inner coats of the mucosa and submucosa are replaced by naked granulation tissue, and only small remnants of the mucous membrane are left together with irregular islands or bridges of swollen mucosa (Plate IV, 3, facing p 68). The outer coats of the colon are affected to a lesser degree the muscularis being oedematous and hyperæmic. In rare cases pericolicitis may appear or pericolic abscesses with perforation. Even in very acute cases with severe destruction, there are islands of mucous membrane in the descending and iliac colons which appear to have escaped almost entirely (Plate XV, 2-4).

The sequence of changes in the mucosa can best be appreciated by systematic sigmoidoscopy (see p 447). According to Bargaen, digital examination in the early stage of the disease gives the sensation of a soft and velvety mucosa with some narrowing. The knowledge of pathology derived from post mortem examinations appears to be misleading the large, shaggy, destructive, and sometimes penetrating ulcers being merely terminal phenomena. A narrowing of the lumen of the bowel is noted extending from the anus. The disease appears to begin in the rectum and spread upwards, the most distal portions of the bowel being involved, the cæcum may be only slightly affected. But, although in 95 per cent of patients, according to J A Bargaen's statistics of 1,500 cases, the disease process begins in the rectum it may commence anywhere in the large intestine, sometimes even in the cæcum, and the pathological picture is the same whatever portion of the bowel is involved.

Thickening of the bowel wall is almost invariable. In the acute stage it is caused by oedema and infiltration of blood and inflammatory exudate, in the chronic stages by the deposition of fibrous tissue. Some authorities, notably W W Soper (1916) have called attention to the increased amount of fat in the wall of the colon but this appears to be an exceptional condition.

Injury to the nerve supply of the bowel (notably in Auerbach's plexus) undoubtedly results from such extensive inflammatory changes and this may be responsible for the increase of peristalsis of the gastrointestinal tract which is so outstanding a clinical feature of the disease.

Inflammatory polypi, formed of granulation and fibrous tissue substances covered with columnar epithelium, are a feature of the terminal stages of ulcerative colitis. Adenomatous changes may occur, producing the condition known as pseudo-polyposis, to be

distinguished from genuine polyposis (*see* p 486). During the healing process an irregular, scarred, fibrotic bowel wall with bridges of unhealed and healing mucosa is to be found. In the final stages the pathological picture closely resembles that of similar stages of bacillary dysentery.

S Lups (1935), and others have called attention to shrinkage and shortening of the large intestine. This occurs particularly in the descending colon, but in a few cases the cæcum and ascending colon are affected.

H G Rudner (1935) considers that the regions of the intestine are affected in the following order: pelvic colon and rectum, descending colon, cæcum and ascending colon, transverse colon and terminal portion of the small intestine.

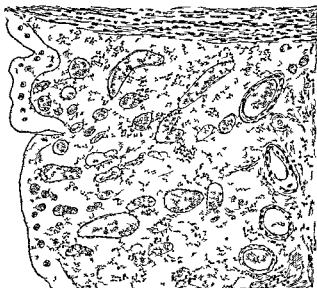
The *microscopic pathology* naturally varies very much according to the stage to which the morbid changes in the bowel wall have advanced. The earliest changes appear to be caused by emboli and infarcts in the wall of the colon accompanied by dissolution of the mucosa immediately adjacent as noted by L A Bue and A A Humphrey. The earliest microscopic changes recognizable are small lesions associated with oedema and hæmorrhage. At the base of these areas, deep in the mucosa and submucosa, capillary vessels are occluded by hyaline masses. The relation of the hæmorrhagic lesions to the occluded vessels is noteworthy, for scattered among the myriads of these lesions are areas where there is occlusion of the capillary vessel and no evidence of any pathological changes in the adjacent mucosa. In the ulcerated stage large numbers of diplostreptococci and other micro organisms are observed in the walls of the colon, and Vimtrup has noted at the edges of the ulcers masses of leucocytes and a zone of fibrinoid necrosis. The muscularis is well preserved and the serosa is affected in varying degrees being as a rule hyperæmic (Fig 76).

The writer has paid special attention to the histopathology of ulcerative colitis and has taken every opportunity to examine the intestinal tract of fatal cases as well as specimens obtained from various hospitals and institutions. He has also compared the histology with that of a parallel series of proven cases of bacillary dysentery. As a result of this study he regards the histopathology of ulcerative colitis as distinctive and differing from that of the other disease. The following are the main points.—In ulcerative colitis the onus of the pathological changes falls upon the submucosa, and the earliest changes are to be seen in the blood vessels which are grossly distended and, in some instances, thrombosed. The process appears to commence in the submucosa, the mucosa being secondarily affected. Cellular response is much less marked than in bacillary dysentery and the cells of Auerbach's plexus are specially attacked.

*Biochemical observations*.—R Goiffon has studied the biochemical aspect of the disease, but his observations do not go far to clarify the situation. He finds that the biochemical picture is dominated by the

alterations in the stools and the abnormal products which are derived from the ulcerated areas. In the faeces putrefaction gives rise to amino acids and to ammonia, which renders them alkaline.

**Age-incidence**—Lockhart Mummery and others agree that ulcerative colitis is a disease of early adult life. Out of a series of sixty cases, the average age was thirty seven. The decade in which onset most frequently occurs is between the second and third, the next most common, between the third and fourth. In children, the prognosis is especially bad, but J A Bergen and J W Kemble hold that below the age of twenty, ulcerative colitis is rare. They had one patient under nine



P H M E

Fig. 76—Microscopic section of ulcerative colitis showing destruction of mucosa with vascular engorgement and cellular reaction in submucosa.

years of age and three between ten and nineteen years. D C Hare has published figures which more or less agree with the above. The sexes appear to be about equally affected.

R J Jackman, I A Bergen and H F Helmholz (1940) have carried out a comparative study on a statistical basis on a group of ninety five children out of a whole series of 871 patients. They find that chronic ulcerative colitis is not rare during infancy and childhood up to the sixteenth year as has been generally believed. In fact taking the group as a whole, it was found that 10.9 per cent had been afflicted with ulcerative colitis since childhood.

As compared with the adult group more children have severe or fulminating symptoms at the onset of the disease.

**Symptoms and physical signs.**—This variable and polymorphic disease may in its insidious onset appear to be quite innocuous, or it may occur with dramatic suddenness and be rapidly fatal, sometimes it is apparently the sequel of some infectious illness such as influenza, or of infections of the upper respiratory tract, as frequently emphasized by Bergen. The connexion of extremely serious and rapidly fatal cases with bodily trauma or injury has been noted by various writers, notably by H. Fagge who recorded the case of a man of twenty who, having sustained concussion in a street accident, died of ulcerative colitis after a comparatively short illness of six weeks. He recorded also three other fatal cases which followed extraction of teeth, and Hale White one associated with fracture of the femur.

There are cases in which the preliminary signs and symptoms are generally recognized as those of mucous colitis—that is, the patient has a peculiar introspective psychological make up, is subject to indefinite and variable abdominal pains, and passes large amounts of mucus in the fæces—which gradually merges into chronic ulcerative colitis. The writer, while acknowledging that this mode of onset is uncommon, has records of three such instances.

The mildest forms of this disease are at first unaccompanied by any noticeable systemic disturbances. The patient, usually a young woman in apparently good health and condition, complains of the passage of blood or blood stained mucus with formed stools every morning, unaccompanied by pain, straining, or any signs of distress. According to E. T. C. Milligan, this peculiar state, which is known as *granular proctitis* or *rectitis*, may be an independent condition, and the patient may not suffer from any further complications. On the other hand, the writer has observed three cases in which this granular condition of the rectum constituted the starting point of more extensive disease of the colon.

He nevertheless believes that Milligan's view is correct and that a strictly localized, independent, granular condition of the rectum exists, and can persist unchanged for years and be compatible with good health. He has now observed one case continuously for seven years in which the condition has varied from time to time and the mucous membrane has exhibited small superficial ulcers. Apart from some rheumatic pains in the knees, the patient, a woman of thirty nine, has remained in good health. There are now no signs of anæmia and she has put on over 28 lb. in weight, but there is a discharge of blood and mucus almost daily with the stool, sometimes it precedes, sometimes follows this evacuation.

In granular proctitis the discharge of blood and pus may be very profuse and apparently out of all proportion to the severity of the lesions seen by proctoscopy. The appearance of the rectum, when viewed through the proctoscope, is velvety, moist, and granular. It is easily traumatized and the normal branched blood vessels are no longer visible. Shallow pitting may be present, but there is no deep

ulceration The discharge on the surface varies from a trace of blood stained mucus to large quantities of muco pus, and the mucus secreting glands are not totally destroyed

In ulcerative procto colitis, on the other hand, the whole thickness of the mucous membrane, with its tubular glands, is destroyed in localized areas, so that eventually the ulcers have irregular edges with the circular muscle exposed This ulcerative type is rarely confined to the rectum, but invades the colon and is not so common as the granular type

The end results of inflammation are different in the two types In the granular form resolution is complete and the mucous lining is restored to normal, but in the ulcerative form, complete healing is never established—in fact a granulation polyposis may develop Ulcerative procto colitis appears to be but a localized form of true ulcerative colitis The patient's appearance due to the toxæmia is typical There is secondary anæmia, loss of weight and continued pyrexia

The question has been raised whether a gonococcal infection of the mucosa may not produce a condition resembling granular rectitis The author has made frequent attempts to demonstrate intracellular diplococci in scrapings from the ulcerated rectum but without success

In 1928 the author saw a man twenty nine years of age who had contracted a rectal gonococcal infection in India He exhibited blood stained purulent discharge from the rectum in which numerous gonococci were demonstrated When examined after an interval of four months the appearance of the mucous membrane resembled that of granular rectitis He was treated by protargol suppositories and eusol lavage combined with protein shock therapy which finally cured the condition

All who have written on this subject emphasize the difficulty of associating the mild with the very severe cases of the disease Whether the mild forms are always identical with Milligan's granular proctitis is a matter for speculation E D Kiefer considers that blood loss may be so slight that the patient is unaware of the presence of blood in the stools

In the *acute form* the patient may awaken with sudden abdominal pain colic and diarrhoea resembling acute bacillary dysentery In other cases it may commence as a simple diarrhoea which rapidly becomes exacerbated The motions are very fluid and contain as a rule, little faecal matter but large amounts of mucus and blood in varying degrees Abdominal pain is severe and in the early stages temporarily relieved by the passage of stool Occasional vomiting is also a feature, nausea and severe epigastric pain occur These cases are usually accompanied by an irregular pyrexia which becomes progressively more marked but on the other hand they may be apyrexial The symptoms usually advance rapidly and cases may vary widely in severity In the most acute cases the patient gradually becomes more and more emaciated and toxæmic, with constant passage of blood stained stools, and dies from exhaustion in two to

three months. A certain proportion, however, after temporary improvement, drift into the chronic form.

In the *chronic form* there is persistent diarrhoea which varies little from day to day, there are practically no remissions, or periods during which a solid motion is passed. The faeces are often soft and brown, there are no solid particles, and mucus and blood are present in a varying degree. Gastric symptoms are usually absent—there is no nausea, vomiting, or flatulence, unless they are produced by an unsuitable diet but haematemesis may occur. The tongue is clean, and the appetite remains fair until the terminal stages. On examination the abdomen is navicular the colon tender and, on palpation, the sigmoid colon is found to be spastic. Some of the cases progress favourably, though complete recovery is rare, the colon being, as a rule, permanently damaged. Acute exacerbations may occur with fatal termination or a severe progressive secondary anaemia may develop which may assume the pernicious type.

In those cases in which the disease is progressing, a morbid body-odour may be noted to which Bergen has drawn attention. This is usually associated with a hopeless and anxious facial expression. Cramps of legs and arms are not uncommon.

*Regional ulcerative colitis*—B. B. Crohn and A. A. Berg and also A. F. Hurst have drawn attention to a form in which definitely limited areas of the bowel are affected, usually the descending colon or the sigmoid, the mucous membrane in the lower part of the sigmoid and the rectum being entirely unaffected.

N. H. Farley has permitted me to quote the case of a man of thirty two, who had suffered for six years from mild symptoms with occasional exacerbations. A perfectly normal rectal canal and sigmoid was revealed by sigmoidoscopy, and X rays after a barium enema showed that a condition of pseudo polyposis was confined solely to the descending colon. It is in cases of this description that partial colectomy has proved successful. (Plate XVI.)

A. F. Hurst and F. A. Knott (1939) have described such a case with severe ulceration and polyposis extending from the end of the transverse to the end of the iliac colon. This portion was excised and an end to end anastomosis successfully performed.

In this type of case the patients usually do fairly well, though complete recovery is rare because the colon is permanently damaged. Nevertheless, however favourably the patient appears to be progressing there always remains the danger of acute exacerbations which may cause death in two or three months.

A feature of regional ulcerative colitis is that, despite the train of distressing symptoms, the tongue remains clean and the appetite fair. There is usually little abdominal discomfort, apart from continuous diarrhoea, although deep pressure over the course of the large intestine may elicit tender spots especially in the sigmoid colon which is usually palpable and spastic.





3 Photos I G Mack Co. Inc.

1 Radiograph of barium enema in acute ulcerative colitis showing complete disorganization of mucous membrane (Death six months from onset) 2 Barium enema of ulcerative colitis showing ulcer niches in rectum and mottling indicating polypoid condition and attempts at repair 3 Barium enema of ulcerative colitis subsequent to ileostomy to show stenosis and contracted polypoid colon

## ULCERATIVE COLITIS

PLATE XVII



Barium enema of pseudo polyposis secondary to ulcerative colitis showing characteristic mottled appearance and sacculcation of colon



Barium enema of chronic tuberculous colitis (TB in faeces) showing smooth outline. Note Stierlin's sign in the caecum. Reflex flow from caecum

## ULCERATIVE COLITIS

## TUBERCULOUS COLITIS

**Complications**—The complications of ulcerative colitis are many and serious. Brust and Barger call attention to a polypoid condition of the colon which follows ulcerative colitis, in a review of 693 cases, they noted the presence of pseudo polyposis in 10 per cent, but a further study of the pathological changes in the colons of forty three patients with chronic ulcerative colitis indicated that the development of true adenomata is frequent. Gallart Mones and Sanjuan have recorded the following complications: diffuse polyposis, stenosis of the rectum and sigmoid, and perforation. Extracolonic complications include arthritis, perirectal abscess, multiple fistulae, ulceration of the skin, and phlebitis.

Among the 693 cases at the Mayo Clinic, there were sixty nine with adenomatous polyposis, fifty nine with strictures, twenty six with perirectal abscess, eighteen with perforation, thirty with arthritis and fifteen with carcinomatosis. Two cases were observed in which carcinomata developed from rectal polypi (Barger). Independent observers, such as W. I. Wheeler, W. W. Soper, and K. Justi (1921) have noted the same sequence of events. R. J. Jackman, J. A. Barger and H. F. Helmholtz found the incidence of carcinoma of the large intestine was 3.2 per cent for their entire group but double that for one series of 95 patients in whom colitis began before the sixteenth year.

Barger has also recorded nephrosis, endocarditis, splenomegaly, ocular disease, hæmorrhage, mesenteric thrombosis, and tetany, multiple complications frequently occurring in the same patient. This same authority has also noted cutaneous lesions, and Ramel has recorded a case in which multiple cutaneous ulcers ran a parallel course to a very severe attack of colitis, they were regarded as the outward expression of severe cytolytic changes in the bowel wall. I. R. Jankelson and C. W. McClure (1940) found skin ulceration in seven cases during the height of an exacerbation, all were febrile and toxic. Lowered resistance to infection plays an important part in their ætiology. Local sulphonamide applications resulted in rapid healing. Ulceration of the stomach with gastric hæmorrhage is rare (Heinz).

**Carcinoma**—Carcinomatous changes in a colon already the seat of chronic ulcerative colitis are frequent as compared with its occurrence in persons giving no history of any infection. Such microscopic studies as have been made suggest that there is a transition from the adenomatous polypus to carcinoma.

The author has recently had a rapidly fatal case of ulcerative colitis in a man of thirty seven in whom active carcinomatous changes were taking place in the fundi of the glands already partially destroyed by the colitis.

**Ocular complications** have been noted by B. B. Crohn in the form of conjunctival and corneal inflammation, a condition resembling xerophthalmia.

**Pseudo polyposis**—A polypoid condition is a common sequel of partial or complete healing in chronic cases, and has been met with frequently since first described by A. F. Hurst. The structure of these

polyp is not that of a true adenoma, and the condition should better be termed *pseudo polyposis*, and must be distinguished from true polyposis (p 486). A point which has been insufficiently emphasized is that pseudo polyposis may develop in the colon in the absence of any marked symptoms of evident ulcerative colitis.

The author (1938) investigated a case in a young man of twenty years of age who was admitted to hospital in a state of extreme emaciation and anemia, the cause of which was found by sigmoidoscopy and radioscopic examination to be pronounced pseudo-polypoid. In this instance there was a previous history of abdominal pain of twelve weeks' and of diarrhoea of one week's duration only.

*Strictures of the colon* are also not uncommon. They may develop, without any change in the symptoms, in the course of healing of a chronic case. Sometimes, when a stricture occurs in the rectum—one of the most frequent complications resulting from long standing involvement (Kiefer)—it may be recognized by sigmoidoscopy, but more usually it is seen by X rays after a barium enema, when two or more strictures may be revealed. (See Table III p 18.) Strictures of the ano rectal region occur in about 9 per cent of cases (W D Smith and R J Jackman).

*Peri rectal abscess and fistulae* may develop as the result of infection of the anal crypts, and generally occur during the active stage of the disease. The former is usually fatal. W D Smith and R J Jackman (1940) have found anal abscess and fistulae a fairly common complication in 8.4 per cent. The indications for surgical interference in the treatment of anal conditions complicating chronic ulcerative colitis should be limited to emergencies such as formation of an abscess.

*Perforation of an ulcer* has been recorded in 3 per cent of the Mayo Clinic cases, but the Guy's Hospital statistics give a higher percentage.

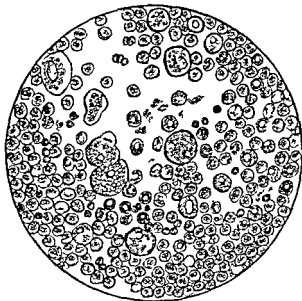
*Multiple arthritis* as in bacillary dysentery, is not infrequent. It occurred in 4 per cent of the Mayo Clinic cases. The author has seen it in three cases, accompanied by fever and affecting numerous joints for periods of two to three weeks. It does not respond to salicylates.

**Diagnosis**—The diagnosis of ulcerative colitis and its differentiation from other diseases, especially from chronic bacillary dysentery, is not always easy. Every aspect of the case, both clinical and laboratory, must be taken into consideration. Pseudo polyposis has also to be distinguished from polyposis. As a rule, the blood sedimentation rate is high in the former and low in the latter.

The bacteriological investigations of typical stools containing blood and mucus are negative. Very often streptococci (*Strept. brevis*) are numerous, and they must be regarded as a concomitant infection, then there is the diplostreptococcus of Bargen, for which special search is necessary (see p 435). The macroscopic characters of the stool vary from day to day and from hour to hour. The faeces consist to a great extent of blood and mucus the former usually predominating.

Very offensive liquid faeces are present intimately mingled with the blood and mucus but except as the result of special medication solid lumps of faeces are never observed. This is an important diagnostic fact. Very often the stools are dark and fluid so that the presence of blood and pus cells can be determined solely by microscopic examination. The presence of pus in the faeces serves to differentiate it from true polyposis.

*Cytodiagnosis*—The microscopic characteristics of the exudate of acute ulcerative colitis cannot always be distinguished with certainty from those of bacillary dysentery. There is a profusion of pus cells



P H M B

Fig 77 —Cellular exudate in acute ulcerative colitis showing pus and large macrophage cells.

with fragmented nuclei. red blood corpuscles are present in clumps or rouleaux. there are also large hyaline macrophage cell (Fig 77) and Charcot Leyden crystals are frequently encountered.

*Digital examination*—Rankin, Bagen and Buie emphasize the importance of direct digital examination. The patient should be placed in the knee-chest position and the lubricated finger should be inserted full length with the flexor surface towards the bladder. The finger should be rotated gently one half turn when the tip will come into contact with the narrowed rectal lumen and register a sensation of stiffness. In early cases the diffusely granular mucous membrane and in later cases disseminated mucosal protrusions can be felt.

*Intradermal tests*—M. Paulson (1937) has drawn attention to an

intradermal test which he believes to be of use in reaching a diagnosis. An antigen from the intestinal surface has been prepared which is allied in some way or other to that of venereal lymphogranuloma. Some cases give a positive reaction with the Frei antigen, but this is not to be taken as an indication that ulcerative colitis is of the same nature as lymphogranuloma. The antigen is prepared by making a lysate from the diseased mucosa with azochloramide in 1:10 dilution. Of this, 0.1 c.c. is injected intradermally.

*Radioscopic diagnosis*—A study of the essential pathological change which affects all layers of the bowel wall will lend significance to the radioscopic appearances. In nearly 80 per cent of cases of ulcerative colitis there are lesions of the large intestine extending above the sigmoid flexure and the radioscopic relief of the damaged mucosa becomes more evident and gross as the inflammatory reaction is more intense.

In preparing the patient for radioscopy, H. M. Weber (1930) has emphasized the necessity for cleansing the bowel of excessive quantities of gas, intestinal secretion and faecal matter. A mild, non-saline cathartic drug, given the evening before, should be supplemented by a few warm enemata of physiological saline solution. S. Lups considers that the evening before the examination the patient should be given a warm enema of 1½ litres of saline.

A barium enema should be given, a thin emulsion of barium being used at body temperature. As it enters the bowel attention should be directed to the rectum for the disease may be confined to this portion only. In early cases no marked radiographic changes may be observed; the only sign may be extreme hyper-irritability, the enema not being retained long enough to permit filling of the colon. The ampulla of the rectum is narrowed and shows a series of coarse and linear striations and as the disease progresses the characteristic thickening, contraction and shortening takes place. In advanced cases the colon fills very rapidly and the ileo-caecal valve is soon reached and sometimes fills. The colon itself is narrowed in calibre and its length is reduced (H. M. Weber). The course becomes straight and the angles at the flexures are converted to right angles. From a soft-phable thin-walled tube it becomes an inflexible, stiff and strait channel giving a picture not seen in any other disease of the colon. Occasionally the colon resembles a string of sausages in appearance owing to contractions which may be due to localized organic strictures or temporary spasm. When the destruction of the mucous membrane is superficial the contour of the colon may be smooth (loss of haustration); when deeper and when real ulceration is present the outlines are ragged and when the ulcerations are very deep many niche-like projections are seen extending out from the bowel. (Plate XVII, 2)

A typical radiographic appearance in one or more isolated segments of the colon with negative results in the recto-sigmoid may give rise to confusion in that it may resemble the changes seen in tuberculous

colitis (see p 499), or even in malignant stricture. This form is known as regional, segmental, or migratory colitis and is more difficult to recognize than is the usual type. It is rare but undoubtedly does occur, its full significance has been emphasized by Bargen and Weber.

The irritability of the affected portion of the bowel, which has been referred to by all writers on this subject, is responsible for "Stierlin's sign"—that is, the shadow of the contrast mass in the normal segments of the bowel is much more intense than in the diseased portion.

In the terminal stages, stenosis of the colon becomes extreme and there is formation of adeno papillomata (pseudo polyposis) (Plate XVIII, facing p 449). By the decompression relief, or Fischer's method, the situation of these granular masses and the occurrence of numerous filling defects can be determined. After expulsion of the enema, air is introduced into the bowel and films are then taken. These reveal a spotted or marked appearance. Sometimes the film gives the impression of a braided band, and the contrast mass attached to the inner half of the bowel may resemble trellis work (Lups) (Plate XVII, 3).

*Diagnosis by sigmoidoscopy*—Sigmoidoscopy judiciously performed, affords a valuable means of making diagnosis certain, and is the only method by which the varied changes in the mucosa may be systematically observed.

H F Bayard (1933), L A Buie and J A Bargen, and others have drawn attention to the fact that the lesions seen at autopsy do not by any means represent the essential lesions of ulcerative colitis and that the true sequence of events can be gauged solely by means of systematic sigmoidoscopic examinations. The ulcers which appear on the mucosa as a terminal event are regarded by most authorities as a secondary infection.

Bayard describes the following characteristics—

- 1 Glazed granular mucosa which bleeds easily when traumatized
- 2 Tubular contraction and thickening of the bowel and rectum (Plate XIX, C)
- 3 An ironed out or rounded appearance of the valves of Houston

T H Morrison (1935) distinguishes the following stages—

- 1 Diffused hyperæmia (Plate XIX, B)
- 2 Edema throughout the involved area associated with thickening and friability of the mucous membrane (Plate XIX, D)
- 3 Formation of milium abscesses which discharge abundant pus (Lups)
- 4 The rupture of these abscesses leading to milium ulcers (Plate XIX, E)

The author's view, based upon his own series, is in full agreement with the above, but in his experience the very earliest lesions observed consist of petechial hæmorrhages into the mucosa, giving an almost purpuric appearance on the normal pale background.

S Lups has emphasized the large amount of pus which, out of all proportion to their size, may exude from milary abscesses. It is a fact that the amount of pus which wells forth from the ulcerated surface is often so large that it gives the impression that a large pericolic abscess is situated in the neighbourhood of the sigmoid and is discharging its contents into the lumen of the bowel.

In the author's experience, sigmoidoscopy is not particularly painful in the earlier stages of this disease, so that no special precautions are then necessary. It is only when a degree of stenosis has taken place that dilatation of the rectum becomes painful.

In concluding the section it should be noted that there are some authorities, notably H. L. Tidy, who deprecate the routine use of sigmoidoscopy and radiology in diagnosis, on account of the irritation to which they may give rise. Tidy considers that the diagnosis is so easily made on clinical grounds that recourse should not be had to any other method.

*Differential diagnosis*—The differential diagnosis has to be made from all other dysenteric diseases in which blood and mucus is abundant in the stools. The difficulty arises chiefly with bacillary dysentery of the subacute or chronic form. The main points are set out in Table XV, p. 449.

#### TREATMENT

The presentation of a balanced and practical guide to the treatment of this disorder involves greater difficulty than is encountered in the whole range of the dysentery colitis group. As F. W. Rankin, J. A. Bergen and L. A. Bue remark (1935): "There have been almost as many types of treatment in chronic ulcerative colitis as there have been contributors to the literature of the subject—a statement with which few will disagree."

In the main, those who have been especially active in the treatment of chronic ulcerative colitis can be divided into three groups: 1, those who believe that the condition is an infective process and advocate its treatment as a chronic, severe, and debilitating infection; 2, those who believe that it is metabolic in origin and who search for some underlying deficiency; and 3, those who believe "colitis gravis" to be a surgical problem.

The old saying that "affections of organs above the diaphragm tend to optimism, and those below to pessimism" was never better exemplified than in ulcerative colitis.

*'Serum and vaccine treatment'*—Since 1923 Bergen has been the protagonist of treatment based upon the consideration that ulcerative colitis is an infectious disease of the large intestine, and he has apparently had great success in using his particular methods. In 1928 he advocated immunization against the causative organism, the removal of all foci of infection, and a liberal high vitamin, high calorie diet. Vaccines prepared from the diplostreptococcus of ulcerative colitis have been used successfully by W. W. Soper, W. Z. Fradkin and I. Gray, H. Surmont and R. Buttiaux. A. J. Chisholm, E. Horgan



TABLE XV—DIFFERENTIATION OF ULCERATIVE COLITIS FROM BACILLARY DYSENTERY

## IDIOPATHIC ULCERATIVE COLITIS

449

	CHRONIC BACILLARY DYSENTERY	IDIOPATHIC ULCERATIVE COLITIS
Onset	May be acute at first often running a relapsing course Evidence of definite infection	Sudden with sweats of infection
Pyrexia	Irregular pyrexias but usually apyrexial	Usually intermittent, pyrexia in bouts
Course	Chronic	May be acute or chronic
Complications	Polyarthritides parotitis	Polyarthritides, polyposis of colon stricture endocarditis septicaemia peri rectal abscesses ulcers splenomegaly
Blood	No anaemia at onset eventually anaemia Serum usually agglutinates Shiga or Flexner bacillus	Very severe secondary anaemia from onset No agglutination
Signs	Usually no tenderness over bowel Defecation very painful	Great tenderness Defecation usually painless
Pathology	Serpiginous ulceration of large intestine localized forma tion of granulation tissue	Commences in rectum degree of ulceration varies greatly in different stages of the disease
Microscopic	Chronic diarrhoeic stool with undigested particles occasion ally blood and mucus	Red blood cells in clumps Disintegrating pus cells and intestinal epithelial cells
Sigmoidoscopic	Bleeding granulation tissue with rigidity of bowel wall	Granulation diffuse inflammation of rectal wall with narrowing of the lumen Miliary abscesses and ulcers
Sequelae	Localized stenosis of bowel B coli complications	Generalized stenosis or bowel perforation haemorrhage in locarditis and septicaemia

and many others. In acute fulminating cases these methods have been reinforced by the injection of specific antibody serum, which has been prepared by the injection of horses with increasing doses of freshly isolated strains of the diplostreptococcus.

This serum (antibody englobulin concentrated serum) has now been administered in approximately 700 cases of chronic ulcerative colitis. It is administered deep intramuscularly, after the patient has been desensitized by small intracutaneous injections. The injection should be given every eight to ten hours, beginning with 0.1 c.c. of concentrated antibody solution, and increasing each injection by 0.1 c.c. until the average maximal amount of 3 c.c. is given. Occasionally only 1 c.c. daily is tolerated, but at other times as much as 5 c.c. can be taken.

In every case in which the serum has been given, there has been a definite improvement in the general condition. The increase of body-weight soon after the institution of treatment with serum has been regarded as significant. There appears to be, also, a definite effect upon the temperature and pulse curves. Although remissions and exacerbations have been the rule in Bargaen's large series of cases, some patients have recovered after one severe attack, and others have had remissions of years' duration. His statistical summary shows that of 472 cases, 352 (74.6 per cent.) returned to their normal occupation, and of these 250 were entirely free of symptoms and, to all intents and purposes, well. Of these 250, in 48 there was no evidence of disease, either proctoscopic or radiological.

There have been singularly few confirmations, in other countries, of the favourable results claimed by Bargaen. D. Smith has obtained satisfactory results in this country; he has given the serum also by the intravenous route. R. Mader, in Glasgow, has treated thirty cases with the vaccine during the last nine years, and the results have been encouraging, only three cases having been refractory to treatment. The author has followed Bargaen's technique in some twenty of his series of forty cases but has been unable to convince himself of the specific effect or of the superiority of this method over blood transfusion. The one exception was the case of a young Scotsman of twenty-six, whom he treated in 1926-27. Although obtaining temporary relief from blood injections and protein shock therapy, he was eventually cured by injections of the vaccine of Bargaen's diplostreptococcus given over a period of one month.

**Blood-transfusion.**—Rankin, Bargaen, and Buie administer blood-transfusions in acute, fulminating cases, and consider it wise to give relatively small quantities of blood—from 200-300 c.c.—at intervals of three to five days. They regard this as a subsidiary measure. With this most authorities appear to be in agreement, but believe that blood transfusion, especially if followed by a rigor, acts by virtue of a kind of anaphylactic shock.

H. Kalk, observing a case of serum anaphylaxis after the injection of antidysenteric serum, resolved to try the effects of blood transfusion in five cases. He considered his results were very good, varying in accordance with the strength of the resulting reaction, and cites one special case where two transfusions were of little avail while the third, which caused a rigor, was successful. He is, therefore, of the opinion that it is necessary to give large blood transfusions and to produce an artificial serum sickness.

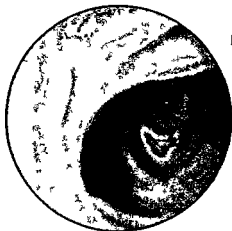
## PLATE XIX

### SIGMOIDOSCOPIC APPEARANCES

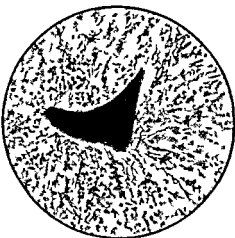
- A **Acute Ulcerative Colitis.**—Showing plum coloured, easily traumatised mucosa in the second stage
- B **Tuberculous Ulceration of Rectum** —Case in which tubercle bacilli were found in material obtained through the sigmoidoscope. The patient was suffering from chronic diarrhoea with blood and mucus in the stools
- C **Acute Ulcerative Colitis.**—First stage. Usually called haemorrhagic colitis
- D **Ulcerative Colitis** —Superficial ulceration in the third, or ulcerative, stage
- E **Mucous Colitis**, showing the pale colour of the mucosa and the masses of adherent mucus
- F **Acute Ulcerative Colitis** —Early stage, showing granular mucosa, with purulent exudate covering the surface. Note the lack of normal folding of the mucosa



A



B



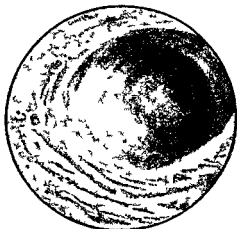
C



D



E



F

*P H N B del*

**SIGMOIDOSCOPIC APPEARANCES**

T Sinek writes that in colitis gravis the beneficial effects of blood transfusion were first noted by Rachwalshy and H Strauss and that this form of therapy has been employed in Austria and Germany by Dzialeszynski Meyer Hensle Bucking and Elias. In his own series eight very serious cases were treated by transfusions of 40-400 c c of blood and the results were most favourable in those cases in which the consequent reaction was most severe.

The writer considers multiple blood transfusions to be a valuable therapeutic measure. He has had some good examples of its beneficial effects in his practice (summarized on p 463). H L Tidy who has adopted a sceptical attitude regarding medicinal measures in this disease recognizes the value of blood transfusions. L A Hulst and H A P Hartog in describing four cases treated by multiple blood transfusions emphasize that it is necessary to repeat the injections if improvement is not rapidly apparent it being advisable then to employ blood from another donor. E Jacobsohn has confirmed the good effects of blood transfusion especially in conjunction with non specific protein shock therapy. He employs for this purpose Pyrifur (an emulsion of *B coli*) given intravenously. A strong systemic reaction is followed by favourable results.

*Autolamotherapy* has been practised for some years with apparent success by R Bensaude P Onry and H Danz. For this purpose 10 c c or more of the patient's own whole blood are injected intramuscularly.

*Sulphaguanidine* (see p 94) —Hopes based upon the beneficial results reported in bacillary dysentery have to some extent been realized in the author's recent experience. When given by the mouth in full doses of 6-10 gm daily no striking beneficial results have been observed but when administered in rectal retention enemata (7-10 gm in 7 oz of water suspended with mucilage or gum acacia) it has yielded to the author satisfactory and suggestive successes in 6 recent acute cases. The treatment is repeated daily for 7-10 successive days and the enema is retained usually without difficulty for 6-8 hours the usual precautions are taken such as raising the buttocks with a pillow and tilting the foot of the bed. No preliminary washout is recommended. Nicotinic acid 150 mgm daily is given by the mouth. The most striking effects have been the cessation of blood and mucus in the stools and diarrhoea and the relief of pain. One particularly acute case of five years' duration has now remained free from symptoms for fifteen months. The others have been equally satisfactory. It is advisable to repeat the course after an interval of 14 days.

*Other sulphonamides* —E N Collins (1940) has exhibited sulphanilamide by mouth in non toxic and parenterally in severely toxic cases until the blood level reaches 8-10 mgm per 100 c c. He has given neo prontosil 1 gm before each meal and a total of 5 gm within twenty four hours. Toxic symptoms are relieved by nicotinic acid 150 mgm daily. He considers that sulphanilamide definitely has a place in the treatment of ulcerative colitis.

**Other measures** *Ascorbic acid* (Cevitamic acid Vitamin C) —G Hetenyi has employed large doses of iron by the mouth (e.g. ferri et ammon

cit ), but since 1934 has been treating cases of colitis gravis with ascorbic acid, basing his action upon the excellent hæmostatic effects of this acid and upon the fact that Vitamin C is missing from the tissues. For this purpose 150 mg of ascorbic acid are injected intravenously, at first twice, then once, daily. In four days from the commencement of treatment, the bleeding ceases.

*Mercurochrome* —A. F. R. Andresen and J. B. D'Alhorn consider that injections of mercurochrome intravenously are of considerable value in hastening the healing of the intestinal lesions. For several years they have used it as a routine measure beginning with 15 c.c. of a 5 per cent solution and increasing the dose at four day intervals, until sufficient has been given to cause a reaction of 101–102° F. The effect of this preparation upon the kidneys should, of course, be carefully watched.

*Calcium and parathyroid* —B. Haskell and A. Canterow consider that the rationale of calcium therapy in chronic ulcerative colitis rests on the favourable influence of calcium upon nutritional changes in the tissues, and on its effects upon spasticity and hyper irritability of the colon. They therefore recommend the exhibition of these drugs as a routine treatment. The calcium is administered in the form of calcium gluconate, in doses of 60 grains three or four times daily, 3½ to 4 hours after meals, the patient being cautioned to avoid eating between meals. The parathyroid (parathormone) is injected intramuscularly, the average adult dose being 20 units, and injections are repeated at intervals of forty eight to seventy two hours. There is immediate improvement in bleeding from the bowel, colonic spasm, and hyper irritability. The diet should be non irritating and spasm should be mitigated by doses of belladonna and kaolin. Nine patients in whom this form of therapy had been employed were subsequently observed for periods of two to six years and showed favourable results.

*Sodium citrate and sodium chloride* —J. F. Montague, following the lead given by Butman, Schultz, and Van Kleeck, has for some time considered that there are many points of resemblance between peptic ulcer, especially duodenal ulcer, and chronic ulcerative colitis. He placed patients on a bland dietary from which meat and eggs were excluded. The local preparation of the colon was effected by enemata of clear tepid water given twice daily. Schultz's intravenous solution was given in doses of 20 c.c. twice daily for two days, and thereafter on alternate days. This consists of a combination of sodium citrate and sodium chloride raised to a concentration higher than the specific gravity of normal blood. The results in cases treated by this method are said to have been very favourable. In a few instances Normet's citrated serum, which contains citrates of sodium, calcium, and magnesium ammoniated iron, and manganese was substituted for Schultz's solution.

*Sangostop*, a preparation made from plant hemi cellulose, which is found mostly in the rind of fruit and of which the active principle is *pectin*,\* has been employed by Kothe. It is suggested that the presence of pectin explains the favourable results of apple diet in diarrhoea. It is galactic acid ester, and has the most remarkable hæmostatic effect. It is given as an enema (150 grains to 50 c.c. of water), after which the bleeding is checked, the special preparation Sangostop is given in 20 c.c. doses by intramuscular injection †.

*Aspectin*, or *Nickelpectinate* (Eli, Lilly & Co.) a preparation which has

\* 'Pectin' is a cellular derivative and has a considerable share in the structure of plants. It is to be found in complex combination with calcium in pulpy fruits, such as apples.

† This preparation is obtainable from Coates and Coates, Ltd., 94 Clerkenwell Road, London, F.C.1.

recently been favourably reported upon in America, appears to exert some action in controlling hæmorrhage. The author has noted improvement recently in advanced cases, but the preparation is not by any means agreeable to take and has a depressing effect. In one particularly successful case 2 tablespoonfuls were taken twice daily for 14 days, with the result that the blood and mucus, especially the latter, disappeared and the motions became formed. The general condition improved enormously. The metallic taste can be disguised by mixing with custard or arrowroot. It has a tendency to cling to teeth and gums, which should be cleaned after each dose.

**Zinc ionization**—The zinc ionization method of treatment was first introduced by J C Webb in 1911. He reported upon fourteen cases which were successfully relieved by ionization, the electrode being introduced into the rectum. In 1930 J Burnford gave an account of twenty-eight cases, of which twenty-one were considered "cures," the first of the series being treated in 1923. Appendicostomy had been performed in every instance, the large intestine being irrigated in the meantime with normal saline solution.

**Intrarectal medication.**—Bismuth subgallate (dermatol), on account of its soothing properties and its hæmostatic action, has been employed by many workers as an insufflation or injection into the bowel. It is first mentioned, in 1909, by Hawkins, who used it in the form of enemata with gum arabic and also with iodoform. Suspended in olive oil in a 5 to 10 per cent suspension, it has been much employed by P Lockhart Mummery, who finds it advantageous in small amounts (four to ten ounces), in which quantity it can be retained in the rectum, and apparently can percolate throughout the colon. The author has employed it as a routine measure in recent years with a fair amount of success. The bismuth is deposited as a bland film on the diseased mucosa and acts both as a protective and as a soothing agent.

For granular rectitis Lockhart Mummery has applied nitric acid to the granulations with a fair degree of success.

Plain olive oil warmed to body heat can be employed in the same manner as bismuth subgallate, and can be retained for two to four hours. Cod liver oil, which is said to have a healing effect upon the granulations, has been used in recent years in the same manner, but its rather pungent odour is apt to act as a deterrent. H Gainsborough (1939) has obtained good results in six cases, with resulting remissions lasting as long as two years. The best results were seen in those cases with shortest previous histories. This treatment is combined with Iso gel (Allen & Hanbury) by the mouth. Retention enemata are not commenced till the diarrhoea has been checked with opium. D Smith uses sodium bicarbonate, one drachm to the pint, as a cleansing enema preliminary to running in eight ounces of olive oil. With this he gives one drachm of Magnolax three times daily and full doses of belladonna, sodium bromide, and chloral hydrate to overcome colonic spasm.

Recently J B Eyerly and H C Breuhaus claim to have obtained good results by the injection of aluminium hydroxide and kaolin as a retention enema. The initial dose is two ounces, increased by the same

amount till the maximum of eight ounces is reached. The injections are given daily. The colon is cleansed with a pint of warm water, and this is followed, after an hour, by a retention enema of three to five ounces of kaolin and aluminum hydroxide in 90-150 c c of warm distilled water.

B. B. Crohn and B. D. Rosenak recommend retention enemata of neutral acriflavine in strength of 1:4,000 normal saline as a daily routine, but they add that when it appears to give more irritation than relief it should be discarded. Lups has tried enemata of 2 per cent boric acid solution, potassium permanganate, ichthyol, bismuth carbonate ( $\frac{1}{2}$ -1 per cent), silver nitrate, protargol, and camomile and tannic acid 1:100. In cases of persistent bleeding from the rectum as in the localized stage of granular rectitis, tannic acid suppositories (three grains acid) have been found, in the author's practice, to be most useful.

**Vitamin A**—Rachet and Busson consider the application of carotene an efficacious treatment. It is given in disoxygenated olive oil (Byla), with a few drops of laudanum, in 2-3 c c doses applied direct to the ulcerated surface after a cleansing enema.

**Antivirus treatment**—Antivirus (Besredka) is a filtrate of a medium in which streptococci and staphylococci have been grown for a long time. E. J. Oesterlin, A. W. Johnson, Kinsey and T. Willett have employed the substance as a rectal injection by first cleaning out the bowel with a boracic enema and then running in 15-20 c c of antivirus by means of a rectal tube. The patient should be kept turning from side to side so as to retain the antivirus as long as possible. It is claimed that the substance acts throughout the whole colon, and that fifteen cases have been successfully treated.

**Multiflor therapy**—E. Reye has employed this form of treatment, which was introduced by Nissle of Freiburg. It aims at altering the intestinal flora and also following the idea of Metzgar (1923) at introducing bacteriophage and immune bodies from a healthy bowel into the diseased one. A cleansing enema is given to a healthy person with one litre of water, the result is filtered and the filtrate is given to the ulcerative colitis patient twice daily as enemata of 250 c c each. Reye took pure cultures of *B. coli* organisms from the feces of six normal persons then transplanted them into broth with glucose and injected the cultures as an enema twice daily into the bowel of six patients, who were greatly benefited.

**Additional intrarectal measures**—H. L. Tidy has on several occasions expressed his conviction that on the whole gentle and palliative methods of treatment produce favourable results. The most efficient treatment in his opinion, is the use of starch enemata of 60-100 c c containing 10-20 drops of tincture of opium. Not more than one enema should be given in twenty-four hours, and not more than four a week. These enemata should be continued until the number of stools has been reduced to five or six a day.

In the second stage when the irritation in the colon has been reduced simple colonic washes consisting of 1,200 c c of normal saline are employed. These are run in from a glass funnel not more than one foot above the level of the rectum and should take at least twenty minutes to administer. The injection of them should never be hurried. Three or four of these washes should be given a week.



In the third stage medicated enemata should be employed. Tidy uses albargin in the strength of 1.5 gramme to 800 c c. A simple colonic wash is administered two hours previously. The albargin solution should not be retained longer than fifteen minutes, and not more than three should be given each week on alternate days.

In the after treatment reliance should be placed chiefly on kaolin and char coal as a method of relieving symptoms.

Insufflation of the rectum has been employed, using powders such as the following. Dermatol (bismuth subgallate) fifty parts and tannic acid and sodium chloride five parts each or talcum ten parts with dermatol or xeroform five parts each. Bismuth subnitrate and tribasic calcium phosphate, 1-2 drachms and kaolin, 1 ounce three times daily, are recommended by Bagen. In cases with achlorhydria, diluted hydrochloric acid is used and when the disease is associated with profound anæmia iron in large doses such as ferrum redactum, 9-6 grammes daily (Schotmuller), may be employed. For tenesmus, suppositories containing the following ingredients are recommended —

Ext bellad	0 2	gm
Dilaudid	0 003	"
Ol cacao	2	"
Bals peruv	0 15	"
Ext hamam	0 03	"
Calc chlorid	0 05	"

D C Hare has recorded successful treatment with liver injections combined with massive doses of iron.

*General summary of effects of medicinal treatment*—Amid the welter of therapeutics which have been applied and have already been described, some attempt must be made to lay down certain main lines of treatment. In the author's experience, blood transfusion is of first importance in building up the patient's resistance and in combating both the mechanical loss of blood and the toxæmia. Again and again, it has proved the means of saving the patient's life (see p 463). The best results are undoubtedly observed in those cases in which anæmia is a prominent factor.

The following are the medicinal measures which have been found useful in practice at the Hospital for Tropical Diseases.

*To check diarrhœa*—Kaolin in some form or other probably the best form is Kaylene oil, which contains liquid paraffin and kaolin. Kaldrox (one drachm three times a day) is also a good preparation.

When pain is a prominent feature, opium combined with chalk in the following mixture affords relief —

R. Tinct opu	5 min
Ol ricin	3 min
Mist cret ad	$\frac{1}{2}$ oz

Half an ounce to be given four hourly

R Pulv ipecac co	10 gr
Salol	10 gr
Sod bicarb	20 gr
Bism subnitras	25 gr

In powder form

*To alleviate spasm and tenesmus* the following prescriptions have been found useful —

1 R Tinct bellad	6 min
Sod brom	5 gr
Elix takadiastase sed	1 drm
Mist mag hydrox	1 drm
Aq menth pip ad	4 oz

Half an ounce to be given four hourly

2 R Bism salicyl	15 gr
Salol	5 gr

In powder form three times a day

3 R Pulv ipecac co	10 gr
Salol	10 gr
Sod bicarb	20 gr
Bism. subnitras.	30 gr

In powder form three times a day

4 Starch and opium enema	4 oz
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*To relieve colicky pains and as an antispasmodic* Rivanol retention enemata 4 ounces to be retained one to two hours are useful Rivanol (2 ethoxy 6 9 diamino acridine lactate) is given in a strength of from 1 2000 to 1 500 It is credited with a general antiseptic action on pus producing cocci—strepto and staphylococci It is incompatible with acids and with normal saline

*To relieve flatulence —*

Medicinal charcoal (Bragg)  
Charkaolin (Allen & Hanbury)  
Pepsin bismuth and charcoal tablets (Boots)

*To check intestinal bleeding —*

Tannic acid retention enemata (10 ounces containing 5 per cent tannic acid)  
Tannic acid suppositories (tannic acid 3 grains)

*For anaemia —*

Blood transfusion  
Large doses of iron ferri et ammon cit 30 grains three times daily  
Eatan (a muscle and beef extract made by Fassett and Johnson)  
one teaspoonful in half a tumblerful of water four times daily

*General stimulant —*

Intravenous injections of glucose 5 per cent in normal saline 10 ounces  
Intravenous injections of calcium gluconate (Sandoz) 8 ounces

**Sedatives —**

Chloretone, 10 grains

Tinct opii, 10 minims

Pulv ipecac co, 10 grains

The application of bismuth subgallate in olive oil, especially in chronic cases, has already been dealt with

**Psycho- and physio-therapy.**—The psychological aspects of ulcerative colitis are an important factor, in some cases they almost appear to be the dominant one. A J Sullivan has studied the psychiatric background in eighteen out of twenty five consecutive cases, and in fifteen the emotional disturbances appeared to be of definite aetiological significance. He claims that psychotherapy in most cases produced striking results.

Physiotherapy has also played a rôle. Lups in his summary, claims that it is necessary to give exposures of ultra violet rays sufficient to bring on a reaction associated with erythema and desquamation.

**Dietetic measures**—It has lately come to be realized that starvation diets have no place in the routine treatment of ulcerative colitis. The colon normally functions as a storehouse for substances which are later expelled, the best foods are those which are well absorbed by the small intestine. Some authorities commence treatment of the acute stage by withholding all food for two days. Rankin, Barger, and Buie consider that, in a diet for chronic ulcerative colitis, the main requirements are that it shall be nourishing and of low residue—furnishing from 2,000 to 3,000 calories—and shall be given in as attractive a manner as possible. Milk, it is generally held, is not well tolerated in the acute stages, but can be added later when absorption is better established.

The *bland diet* consists of Cereals, two slices of lean bacon, one egg, toast, butter, and coffee for breakfast. Meat soup, minced meat (liver occasionally), potato, bread and butter, custard, junket, or cornflour pudding, tea, and sugar for lunch. Steamed rice, plain fish and simple pudding for dinner. No fruit or vegetables should be given at first. Beverages should not be iced. Afterwards bananas, vegetable puree, and two glasses of milk may be added.

The German authorities advocate *Moro's apple diet* which is used in persistent acute diarrhoeas both in children and in adults. For adults, seven to twenty medium sized apples are needed per day. They should be peeled and cored, and then chopped up so small as to go brown. Three to ten ounces of this puree are given at each of four meals in the day for two days, during which time no other food at all is taken, except weak tea if the patient is thirsty.

Gradual transition back to normal diet is effected by the following scheme

**Breakfast**—Tea, or cocoa made with water, rusks, stale bread, small amount of butter

**Midday**—Meat broth free of fat, lean meat or ham, puree of potatoes, bananas, rusks, stale bread, cheese

**Tea**—Tea, rusks, small amount of butter

**Evening**—Same as midday

One of these meals is substituted each day for one of the apple meals until the patient is no longer having any apples, and then a slow return to normal diet is made.

A preserved apple powder is sold under the name of *Aplona* \*. This contains an astringent principle and is always ready for use. It is said to exert a specific action on the mucous membrane.

*Salt deficiency in ulcerative colitis*—Salt deficiency is common in ulcerative colitis, as it is in Addison's disease, pyloric stenosis, excessive sweating, diarrhoea and vomiting. C. S. Welch, M. Adams, and T. C. Wakefield of the Mayo Clinic have shown that in ulcerative colitis the deficiency is due to the response of the body to a forced and continuous loss of protein material. In this condition the blood urea tends to be low, pointing to a small catabolism of amino acids and indicating that all the available amino acids are being utilized for the synthesis of the protein which is being lost. The urea nitrogen consequently forms much less than the normal 70–80 per cent. of the total nitrogen leaving the body.

Hence, it is well to point out, a diet liberal in proteins is necessary in ulcerative colitis.

The following is a specimen of *high protein diet* for ulcerative colitis:

#### *First Stage*

*Breakfast*—4 oz. fish, 1 egg and 1 egg white, 3 oz. skimmed milk, bread, butter, tea, sugar.

*11 a.m.*—5 oz. skimmed milk, 1 egg.

*Midday*—5 oz. lean meat, 6 oz. skimmed milk, 1 egg white, potatoes, milk pudding, sugar, fruit.

*Tea*—2 oz. milk, bread, butter, jam, sugar.

*Supper*—5 oz. fish, 6 oz. skimmed milk, bread, butter, fruit pudding (190 grammes protein).

#### *Second Stage*

*Breakfast*—5 oz. fish, 1 egg and 2 egg whites, 3 oz. milk, bread, butter, sugar, marmalade, orange.

*Midday*—4 oz. lean meat, 5 oz. milk, 2 egg whites, potatoes, orange.

*Tea*—1 egg, 2 oz. milk, bread, butter, jam, sugar.

*Supper*—6 oz. fish,  $\frac{1}{2}$  oz. cheese, 1 egg white, potatoes, bread, butter, fruit, orange juice, 5 oz. skimmed milk, 1 egg (220 grammes protein).

**SURGICAL MEASURES**—When medical measures have failed—and this occurs, it must be confessed, in a fair proportion of cases—or when complications ensue, as they so commonly do, then **surgical drainage** must be employed. The nature of this drainage varies according to circumstances.

*Appendicostomy*—The most simple method of obtaining thorough drainage is by appendicostomy, and this operation has been much practised. Alleviation has been observed by the author and many others, this operation affords a method of cleansing out the colon and

\* Coates & Cooper, 94 Clerkenwell Road, E.C.1.

of surmounting a crisis, especially if the drip saline method of continued irrigation is employed. A bed pan, provided with a rubber ring and aperture for drainage, on which the patient reclines, provides a practical means of continuous drainage.

On the whole, modern opinion is averse to appendicostomy, or cæcostomy, as affording insufficient relief to justify their continuation. Also, irrigation of the colon through a cæcostomy opening is not considered to have any special advantages over irrigation through the rectum.

The operation is performed as follows —

1 The peritoneal cavity is opened by a small incision in the right iliac region. A muscle splitting incision, or one at the outer margin of the right rectus muscle with retraction of the muscle inward, may be employed.

2 The appendix is brought through the abdominal wall without damaging its mesentery, and the cæcum near the appendicular base is fixed by two catgut sutures to the parietal peritoneum.

3 The tip of the apex is fixed to the skin of the abdomen as it lies without tension on the abdominal wall.

4 The abdominal wall is closed, taking care not to strangle the appendicular mesentery.

5 None of the appendix is removed, but a rubber appendicostomy catheter is inserted into its lumen, passed into the cæcum, and held in position with a catgut suture.

6 After seven days the unwanted portion of the appendix is excised. An appendicostomy must not be performed if the appendix is fibrosed or very short.

The operation of *valvular cæcostomy* is performed as follows. The operation is performed under local anaesthesia or gas and oxygen. The abdomen is opened by a suitable right iliac incision, and the wound edges are protected by gauze pads. The cæcum is identified and partially extruded through the wound. It may be friable and should therefore be handled with care. This portion is emptied of gas and then clamped by a curved gut clamp. A purse string catgut suture is put into the wall in the region of the anterior longitudinal band in readiness for the catheter. A No 12 Jaques rubber catheter is taken, and an extra hole is cut near the usual opening. The cæcum is opened with the cautery or scalpel and the catheter inserted. The purse string sutures are inserted inverting the cæcal wall like a milk bottle.

Irrigation should be performed twice daily, the best solution for this purpose being normal saline under about  $1\frac{1}{2}$  foot of pressure. It is a good plan to put a rubber tube into the anus and to place the patient over a rubber protected bed pan while the irrigation is being performed, in order to obtain an efficient through drainage.

Surgical operation offers a definite but much debated method of treating ulcerative colitis. It is generally conceded that it should be undertaken only after due deliberation and only in those cases in which all other remedial measures have failed to afford relief. The results are often brilliant, and it is unreasonable to assume that it is not justifiable in any circumstances.

M. Donati considers that ileostomy, cæcostomy, and colostomy of

the ascending colon may any of them be indicated, according to the nature of the case. Partial colectomy can be performed, but total colectomy is absolutely contra indicated.

**Ileostomy**—L S Kilbrick and R H Miller in recording twenty nine recent cases, covering a period of ten years in which ileostomy had been performed, recommend this as the only operative measure which should be seriously considered. Of these twenty nine cases ten have required a further operation of total or subtotal colectomy. The indications for colectomy are said to be polyposis, recurrent attacks of fever, malaise and continued anemia. Both operations—ileostomy and colectomy—should be preceded and followed by blood transfusions.

Bargen Brown and Rankin have reported eighty two cases, ranging in age from seven to sixty one years in which ileostomy has been performed. The most beneficial type is the one barrel ileostomy. They consider the results of this operation to be satisfactory especially when performed to relieve the chronic complications of the disease but they recommend that it should not be performed in uncomplicated cases unless other forms of treatment have been thoroughly tried. From their extensive experience they do not consider that any other operation e.g. appendicostomy, caecostomy or ileo sigmoidostomy give the same result. They have observed that stricture of the affected colon inevitably takes place after ileostomy.

F W Rankin has issued an additional report upon a series of five cases of colectomy for diffuse pseudo polyposis and other complications of chronic ulcerative colitis. In four the colon was removed down to the recto sigmoidal junction and in the other total colectomy was performed. Rectal polypi were treated by vigorous fulguration.

H W Cave and W F Nickel (1940) have reported upon 30 ileostomies with 7 deaths (mortality rate 23 per cent). This rate is as high as 45 per cent in emergency ileostomy. This operation should not in itself be regarded as a curative process, they hold, but as the first step in the complete removal of colon and rectum.

J R Regin and E H Mensing (1932) perform the operation in two stages. Ileostomy is done at the first stage and at the second the ileum is anastomosed to the caecum. Appendicostomy is also frequently carried out to guard against gas tension in the line of the ileo-caecostomy.

D P MacGuire considers that ileostomy should be performed only if the patient and his family fully understand that the opening is to be permanent. He considers that aseptic technique is extremely important as in long standing cases of ulcerative colitis there is a great influx of pathogenic bacteria into the colon and terminal ileum.

R B Cattell considers that transverse ileostomy is the operation of choice and is of great value in chronic cases. W Weissenborn (1939) has reported the successful removal of the colon from caecum to anus. The patient, a man of 18 recovered with a permanent ileostomy opening.

In cases of extensive perirectal abscesses or rectal strictures, colostomy may be required for temporary drainage but usually in

cases of this severity the greater portion of the large intestine is involved, so that eventually ileostomy becomes necessary

**Prognosis** —It is difficult to predict, with any degree of accuracy, the turn of events in a given case of ulcerative colitis. It is such a variable and irregular disease. But, from a study of the figures given during the last twenty five years, it appears that the prognosis in a case of average severity is by no means good.

**Mortality rate** —In a discussion held at the Royal Society of Medicine in 1909, it was recorded that, out of 288 cases collected from the records of seven London Hospitals, 50 per cent had died. In 1928, Bellingham Smith reported that twenty four out of his forty six hospital cases had died (52 per cent). Recent statistics are rather better. According to L. S. Kilbrick and R. H. Miller, who record a series of 149 cases, the mortality rate is 18 per cent. In twenty (74 per cent) deaths followed some operative procedure, deaths also occurred from peritonitis, widespread sepsis, and local disease, such as pneumonia. T. L. Hardy and E. Bulmer record thirty one deaths in a series of 104 cases, seventeen in male and fourteen in female patients and they remark that the survival rate is much improved after the first year and even more so after the second. Of this total, over half died in the first year, 32 per cent in the second, and 17 per cent thereafter.

Lockhart Mummery, in his series of 459 cases had thirty three deaths from the following causes: perforation and general peritonitis, nine; exhaustion, seventeen; septicaemia four; embolism two; and anuria, one. Perforation of the colon constituted one of the commonest forms of death, in two cases more than one perforation was present. Perforation of the ulcer may actually occur without causing general peritonitis.

The expectation of life appears to be fairly good in private institutions as E. I. Spriggs's (1931) statistics at Ruthin Castle show a mortality rate of only about 12 per cent.

A. F. Hurst, at New Lodge Clinic, 1921-34 has treated some forty patients with very favourable results: the mortality rate in this series being as low as 7.5 per cent. He believes that the mortality should not exceed 5-10 per cent of patients receiving adequate treatment. It is doubtful, however, whether the majority of specialists who have had extensive experience in intestinal diseases would agree with Hurst in holding that a large majority of patients with ulcerative colitis, however severe, should recover eventually so completely as to be able to lead a life of normal activity. There is always a very great tendency to recurrence. Relapses are apt to be brought on by superimposed infections, especially tonsillitis, and by fatigue or mental strain. Hurst has pointed out that in younger patients the colon, when examined after giving an opaque enema, may show an abnormal appearance, and yet the patient may not have suffered from diarrhoea for years.

Hurst has given the following table from his own statistics as well as those of L Spriggs

Well or carrying on	66	(77.6 per cent)
Not well	9	(10.6       )
Ill	2	( 2.4       )
Dead	8	( 9.4       )

Of the 66 recoveries, 38 had no relapses and 28 had relapses from which they recovered

*Duration of the disease*—T L Hardy and E Bulmer, in their series of cases from the General Hospital Birmingham found that the case of shortest duration—a fatal case—lasted six weeks and at the other extreme there was a patient suffering from the intermittent type of the disease who succumbed eventually after thirty six years.

According to these authors the most unfavourable type of case is the one showing an acute onset and the most favourable the one characterized by intermittent attacks with complete freedom in the intervals.

*Relapses*—Binks and Barton (1934) discourage an unduly optimistic state of mind when the treatment appears to have been successful at the termination of the attack. The joy of the patient will not be shared by the wise physician who having his knowledge upon the fundamental pathological changes in this disease will realize that the condition may recur.

The histories of 232 consecutive cases of chronic ulcerative colitis in the Mayo Clinic have been analysed. 209 patients had received medicinal treatment and twenty three had been previously subjected to some form of short circuiting operation. In 140 patients no less than 276 recurrences of colitis were noted. Infections of the upper part of the respiratory tract were held directly responsible for the great majority, but an appreciable number (12 per cent) were associated with conditions which traumatized or increased the irritability of the gastrointestinal tract.

Immunization against diplostreptococci was carried out as a routine in the treatment and this appeared to be an infrequent cause of the reactivation of a quiescent colitis. In 33 per cent of patients this occurred before the fourth injection of vaccine usually it followed the first.

Recurrences after abdominal operations were rare but four were secondary to appendicectomy. Twenty three recurrences (8.2 per cent) were associated with allergic manifestations such as hay fever. Some women patients with quiescent colitis passed through pregnancy delivery and the puerperium without unfavourable incidents. In seventeen cases relapses were preceded by bodily injuries chorea acute exacerbations of chronic arthritis etc.

The seasonal incidence of relapses has also been noted, there is a definite tendency for the relapse rate to be lowest in the summer months. The tendency to relapse was found to decrease with age, so that in the same period of time the patient over forty may be expected



to have only three fifths as many relapses as the patient of under twenty

It might be assumed that the more extensive the involvement of the colon, the more frequent the number of recurrences, but there appears to be no rule governing this factor

Once the disease has made its appearance, the mucous membrane and indeed all the layers of the bowel-wall are permanently altered, and in the healing process swellings, polypi, and strictures may form. Even when such strictures interfere with the passage of the normal faecal contents, no special tendency to relapse appears to be induced

As already related, the most important factors in producing relapse are found in infections of the upper part of the respiratory tract, which apparently accounts for the high percentage of them that occur in winter. Attempts to improve matters by removing infected tonsils may only result in bringing about a severe relapse

According to the studies made by E. D. Murray, psychological and hysterical stresses appear also to be predisposing factors during the third and fourth decades of life.

*Summary of the author's series of forty cases of ulcerative colitis (1920-37)*

This resume gives, in succinct form, some of the facts to which reference has been made in the text

Sex males, ten, females, thirty    Average age    twenty to thirty eight, eldest fifty    Deaths in hospital    two (5 per cent)    Residence abroad    nine only, in India, Ceylon, Australia, and South Africa    All clinical degrees of severity were noted

**Pyrexia.**—Majority pyrexial, exhibiting various degrees of fever, four apyrexial. One woman of twenty six exhibited continuous remittent pyrexia (102-103° F) for three weeks after cessation of active symptoms and when stools were normal. No cause for this fever was discovered, but it appeared to be entirely beneficial as the disease, which had lasted for four years, ceased and she returned to Burma in good health (Chart 14)

**Complications** —Arthritis, parotitis, peri rectal abscess (very extensive, fatal), stenosis of bowel, and multiple hæmorrhages

One woman of forty six was treated for four serious relapses within six years, with intestinal hæmorrhages so severe as to imperil life, multiple deep ulcerations throughout the large intestine were seen by X rays after barium enema, fistulae opened into the vagina but healed without surgical interference. She recovered on each occasion after repeated blood transfusions, and is now (1937) well, with no anæmia, or any external symptoms

**Granular rectitis.**—Three cases primarily diagnosed as granular rectitis developed into classical ulcerative colitis

**Operative treatment.**—*Appendicostomy*, two cases, performed 1931 and 1932, both clinical successes, have preferred to keep appendicostomy patent

*Appendicectomy*, one case, in which pathological appendix was demonstrated and removed with considerable benefit to the patient

*Valvular cæcostomy*, one critical case, in a woman of thirty four, who

had suffered for seven years she was 3½ months in hospital and was lavaged daily with six pints of saline through caecostomy opening Great clinical improvement discharge 1 with colotomy belt

*Ileostomy* one very successful case in man of twenty five (Figs 78 79) His illness commenced in South Africa in 1931 with very severe dysentery thought to be bacillary and generalized arthritis In April 1932 he was admitted to hospital with great anemia emaciation (loss of 70 lb) night sweats arthritis Sigmoidoscopic appearances were typical and X rays after barium enema also gave typical appearances In May a complete membranous cast of the large intestine was

April 1934

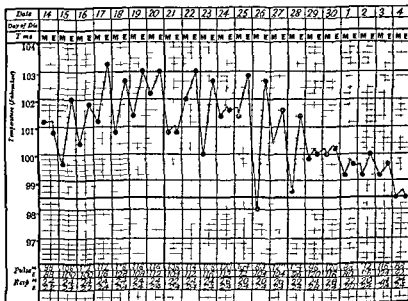


Chart 14 — Pyrexial bout during convalescence from ulcerative colitis The patient remained subsequently free from symptoms for three years (See text)

evacuated Appendicostomy May 1932 gave no relief Valvular caecostomy September 1932 with lavage through the caecum plus bismuth subgallate in olive oil brought about great improvement and an immediate gain in weight Blood transfusions and continuous intravenous drip saline were required periodically as the condition of the patient became critical

It had not been realized at this time how rapidly stenosis of the isolated colon proceeds and after every care had been taken to ascertain the state of the lumen of the colon the caecostomy was closed Three months later when all was apparently going well the acute symptoms returned and the state of the patient once more became critical After a double barrelled ileostomy (March 1934) when it was found that an advanced degree of stenosis of the transverse and

descending colons had taken place the general condition of the patient once more improved and blood regeneration quickly took place. In October 1935 he weighed 12 st 4 lb and was comfortably fitted with a colotomy belt. No excoriation of the skin was noted. In



Fig 78—Very acute case of ulcerative colitis. Appearance of patient three months after ileostomy



Fig 79—Appearance of the same patient before operative treatment

February 1936 he was readmitted with intestinal hæmorrhage, proceeding from pseudo polyp, which had formed in the sigmoid colon and this was checked by tannic acid enemata 1 per cent. Since then he has remained in good health.

Bargen's serum was given continuously and in large quantities in this case and had no appreciable effect upon the disease.

## CHAPTER XXV

### MERCURIAL COLITIS, URÆMIC COLITIS AND OTHER FORMS OF TOXIC COLITIS, INCLUDING THYROTOXICOSIS

#### MERCURIAL COLITIS

MERCURIAL poisoning in its clinical manifestations may be divided into three stages (a) the *acute*, which generally takes place in suicidal cases from an overdose of mercuric chloride (b) the *subacute*, usually occurring from therapeutic overdosage, for example, during treatment for syphilis and (c) the *chronic*, found in industrial workers. A large proportion of those exposed to mercury may be affected, mainly because the adhesion of the metal to the skin and the inhalation of mercury vapour makes efficient protection difficult.

The immediate effects of mercurial poisoning are due to coagulation, irritation and superficial corrosion to which the mucous membranes are susceptible. The objective symptoms are a metallic taste, salivation, burning sensation and, subsequently, ashy discoloration of the mouth and pharynx. Later the large intestine and kidneys become involved and within three days the urine becomes scanty, with albumin and casts. Anuria becomes established and death may ensue within one week.

**Pathology**—The macroscopic and microscopic appearances of the mucous membrane of the large intestine resemble those of severe ulcerative colitis. There is hemorrhagic congestion and coagulation necrosis leading to ulceration. The kidneys exhibit the appearance of acute nephritis often with calcification of the epithelium of the convoluted tubules.

This pathology is interesting in so far as it has a bearing on the etiology of ulcerative colitis.

Thus J. A. Bergen, A. E. Osterberg and F. C. Mann, working on absorption and excretion of arsenic, bismuth and mercury by the colon, found that lesions appearing after intravenous injection of mercury (as in H. M. Baldwin's experiments) are due to actual excretion of the poison through the intestinal epithelium. Possible in addition, the renal lesions predispose to the formation of toxic substances, and it might be inferred that a similar toxin (or toxins) is excreted via the intestinal mucosa in ulcerative colitis.

**Symptoms**—When mercuric chloride is taken by the mouth in doses of one gramme or more, it produces little effect if vomiting occurs within three minutes, but should this be delayed for five minutes, toxic phenomena set in. Other soluble mercuric salts the chloride, iodide, and cyanide have approximately the same toxicity, though the toxicity of organic compounds with firmly bound mercury is relatively low.

Stomatitis is the earliest symptom of excessive therapeutic use or of chronic poisoning. It occurs as readily when mercury is used by ununction or injection as when it is taken by the mouth. Tetter, a metallic taste, soreness of the gums, and salivation (ptyalism), are its accompaniments. If the mercuric dosage is pushed further, the gums blacken and, later again, the tongue swells and ulcerates. In a chronic case of severe poisoning all the teeth may be lost and necrosis of the jaw may ensue.

The mechanism of stomatitis and colitis is thought to be connected with the precipitation of mercuric sulphide which takes place in the capillary endothelium in the mouth and colon, the sulphide being formed by the interaction of putrefying material with the circulating ionized mercury. It is toxic to the cells with which it is in contact, and the injured necrotic tissue furnishes a starting point for ulcerative micro-organisms, especially *B. fusiformis* and *Spirochaeta dentium* and, in the large intestine, *Bacillus coli*.

The symptoms of mercurial colitis may greatly resemble those of ulcerative colitis, there is the same passage of blood stained mucus together with pain and tenesmus. At other times the symptoms are those of a chronic and uncontrollable diarrhoea.\*

In urological literature specific instances are to be found in which symptoms of acute ulcerative colitis have supervened upon some simple urological operation such as cystoscopy. A series of such cases have been reported in recent years. A. L. d'Abreu and A. C. Lyssaght (1936) recorded three. The onset was as sudden as it was unexpected, for the subjects were healthy men without any suspicion of renal inflammation. Two were fatal and the colon showed an extraordinary degree of recent hypertrophic ulcerative colitis, the mucous membrane smelling strongly of ammonia. In a second paper in 1936 these same authors put forward the idea that undue susceptibility to mercury might possibly be the determining cause, as the instruments used at cystoscopy had been previously disinfected in 1 : 8,000 oxycyanide of mercury solution.

This matter has now been finally cleared up by B. H. Page and C. Wilson (1940) who encountered this condition in three patients after cystoscopy in which mercury oxycyanide had been used as a sterilizing agent. In two, diagnosis of mercurial poisoning was arrived at during life and proof was obtained of the presence of this metal in the organs post mortem.

Acute mercury poisoning after cystoscopy might possibly be due to mistaken use of a too concentrated solution, abnormal circumstances leading to excessive absorption, or idiosyncrasy. When the morbid changes in the bladder are unusually severe this may aid absorption. There is now no doubt that oxycyanide of mercury in examinations of the urinary tract is highly dangerous.

\* In lead poisoning the most prominent symptoms are 'lead colic', a paroxysmal pain eased by pressure together with oliguria and obstinate constipation. In arsenical poisoning there is vomiting first and then acute diarrhoea resembling cholera.

**Treatment**—The first essential, when mercury has recently been taken by the mouth is to produce emesis. Milk and calcium sulphide by the mouth should subsequently be given in large quantities, also enemata containing 10 per cent sodium thiosulphate. A popular antidote is three raw eggs and a quart of milk followed by gastric lavage. A hypophosphite peroxide mixture is very effective, sodium hypophosphite, 1 gramme in 10 c.c. of water, and hydrogen peroxide 5 c.c. should neutralize 0.1 gramme of mercuric chloride.

### URÆMIC COLITIS

In the uræmic state whether produced by the intrinsic condition of the kidneys or the accompaniment of some other disease gastro intestinal symptoms are extremely common. Diarrhœa is associated with vomiting, and both the stools and vomit contain considerable amounts of urea. Very often blood and mucus are present in the stools, which then resemble those of a case of acute ulcerative colitis. This is the statement made in most textbooks of general medicine. Little or no original investigation into this infrequent complication appears to have been undertaken.

There is considerable evidence that violent inflammatory disturbances of the alimentary tract do accompany both acute and chronic urinary disturbances. The lesions of the mucous membrane appear to be caused by the excretion of urea through the intestines. In their pathology and general appearance they resemble ulcerative colitis (Plate XV 1 facing p. 484).

### COLITIS FOLLOWING RECTAL MAGNESIUM SULPHATE

In the pre-operative treatment of many forms of cerebral disease with high cerebro spinal fluid pressure for example in brain abscess a 25 to 50 per cent solution of magnesium sulphate is often given per rectum four to six hourly for one or two days with the object of reducing pressure temporarily so that an operation can safely be performed. A certain percentage of such patients develop definite signs of rectal irritation with blood and mucus in the stools. In such an event the administration of magnesium sulphate per rectum must be stopped and it must be given orally if the patient is conscious or intravenously if he is comatose. The last method is not safe, however and should always be avoided if possible. The method of choice, unless colitis supervenes is always per rectum. The colitis takes about three days to subside after medication by this route is stopped.

It is suggested that further investigation of this form might shed new light upon the ætiology of mucous colitis (p. 421).

### ETHER AND AVERTIN COLITIS

The drugs most commonly used per rectum to produce anaesthesia are ether paraldehyde and avertin. That they can produce proctitis or colitis is indisputable and therefore care must be observed in their use and close attention paid to the recognized technique.

**Ether**, as vapour or as liquid dissolved in saline in the form of a rectal application, has fallen into disfavour owing to the difficulty of inducing anaesthesia and to the serious after effects. Dudley Buxton describes the method in detail and writes of such after-effects as 'colicky pains in the intestines, urgent tenesmus, diarrhoea, sometimes dysenteric in character'.

Used as a 5 per cent solution in warm normal saline apart from technical difficulties, more success has been obtained but Arnd describes diarrhoea in his cases.

**Ether in oil** (olive or carron) seems, however, to be free from the objection of causing irritation of the bowel and Gwathmey, using a 75 per cent solution, claims to have had no trouble. Hatcher advocates a 50 per cent solution as the maximum strength on account of the fear of colitis but, from experience of some hundreds of cases, Mennell reports that no trouble need be anticipated in the rectum from the use of a 60 per cent solution of ether in olive oil. The ensuing anaesthesia has, however, to be supplemented.

**Paraldehyde** given per rectum is extensively used as a preliminary narcotic for children, but it is used only in such a way as to induce sleep, anaesthesia then being procured by other means. A 5 and 10 per cent solution in saline is frequently given in doses gauged by body weight. Any proctitis following such doses is negligible, though slight tenesmus has been said to occur.

**Avertin** is nowadays used most extensively and is given by the rectum in a 2½ per cent solution in doses calculated by body weight (0.1 gramme per kilo). It is tribromomethyl alcohol and is unstable in solution, readily decomposing into toxic bromine compounds which are very irritating to the intestine. It must be freshly prepared for every patient and dissolved in distilled water at 113° F (45° C), and the solution must be tested with Congo Red before use. Cooling allows crystals of avertin to be precipitated and warming leads to its decomposition.

If due care is taken in the preparation of the solution, irritation of the rectum very rarely occurs and is then only transitory. In a series of 5 000 cases published by L. B. Mueller there were only two cases of rectal trouble. One was a minor incident but the second was more serious, necrosis of the intestinal mucous membrane being found.

### DISEASES OF THE THYROID

**Thyrotoxicosis**—Among the many clinical manifestations of thyrotoxicosis, chronic diarrhoea is a feature, it may indeed constitute the one outstanding symptom. This is a common experience in the fully developed exophthalmic goitre, as well as in the lesser degrees of thyrotoxicosis. It is found in both sexes. In some cases salivation may be excessive. In the acute form especially when nervous phenomena predominate, vomiting and icterus are associated with the diarrhoea, which often coincides with exacerbations of nervous mani-

festations. It may, however, occur independently. In the most severe type, rapid exhaustion follows upon the passage of numerous diarrhoeic stools as in cholera and dehydration is soon set up. When in doubt regarding the true nature of troublesome vomiting, iodine should be given intravenously, as it is usually followed by amelioration of symptoms.

It cannot be said that there is anything characteristic about the diarrhoea of thyrotoxicosis. The faeces are usually liquid, pale, and offensive. No information of positive importance, except the presence of undigested meat fibre, can be obtained from a microscopical examination nor does sigmoidoscopy reveal any characteristic changes in the mucosa.

A man of forty-eight, who for many years had been known to have an adenomatous goitre which had not given rise to any special symptoms, was referred to hospital with a provisional diagnosis of colitis in February, 1937.

For the last fifteen months he had had diarrhoea two or three times daily, and on this account was suspected of chronic colitis. The diarrhoea accompanied by colic had become almost continuous, and during the last year he had lost 28 lb in weight. Definite signs of thyrotoxicosis were present, there was tachycardia especially on exertion, a soft systolic murmur and a pulse pressure of 80. There was also a faint fine tremor of hands and tongue. The stools were diarrhoeic and pale. On sigmoidoscopy no lesion of the mucous membrane could be observed.

Treatment with small doses of tincture of iodine was instituted with immediate improvement. The diarrhoea ceased, the stools became normal and the patient put on weight at the rate of 3 lb per week.

**Hypothyroidism**—It is not generally realized that hypothyroidism or myxœdema may produce the dysenteric syndrome, but one interesting example of this has been encountered.

In 1924 the wife of an English officer in India was examined. She was thirty-one years of age and had been sent home as a case of chronic bacillary dysentery, as she had been passing blood and mucus with her motions although she habitually suffered from chronic constipation. The outstanding feature of her previous history was the number of miscarriages—she had had four abortions in three years.

It was very clear after a brief examination that she was in a state of hypothyroidism, complaining of chronic aching pain in head and right arm while her knees were so weak that they often gave way on descending stairs. She was also subject to recurring chill-lains. Her face was puffy, hair brittle, lips were slightly cyanosed and nails fragile and longitudinally ridged. Speech was staccato.

The blood and mucus in the faeces were probably derived from stercoral ulceration of the sigmoid and rectum due to the chronic constipation. Extensive necrotic ulceration was revealed by sigmoidoscopy.

Improvement on full doses of thyroid extract 3 to 5 grains daily was remarkable. All signs of myxœdema eventually disappeared including constipation and a month later a second sigmoidoscopy showed that the stercoral ulcers had completely disappeared.



## Affections Resembling Dysentery

## CHAPTER XXVI

### MUSHROOM POISONING (MYCETISMUS); HENOCH'S AND OTHER FORMS OF PURPURA

DESPITE the very considerable consumption of mushrooms cases of poisoning by these fungi are by no means frequent in civilized countries at the present time. In the United States of America, however as well as in Europe, isolated cases of mushroom poisoning, usually due to the eating of poisonous species, are annually recognized.



Fig. 80.—*Amantia phalloides* (Half nat. size)  
(After *Enzyklopädie der Naturgeschichte* von J. E. S. P. Paris)

The earliest recorded instance of mushroom poisoning occurred (fifth century B.C.) in the family of the Greek poet, Eurypides, whose wife, two sons, and a daughter died from this cause. Pliny relates that in ancient Rome two Emperors lost their lives in this manner. Parlet (1793) recorded that in the neighbourhood of Paris there were at least a hundred deaths from this cause every year. In the United States the first cases, reported by Cheney, occurred about 1871.

Mushroom poisoning is due to the ingestion of poisonous fungi of the genus *Amanita* which in some degree resemble the common edible mushrooms. Three particularly poisonous species are recognized —

*Amanita phalloides* (Vaillant E Frès 1821) Quélet 1872 The death cup or deadly agaric — This autumnal species has a wide distribution throughout the world. It is usually found in pine forests and adjoining pastures. Yellow or greenish yellow in colour, the surface of the crown is finely striated and it has a greenish coloured stem. This toadstool has no odour when first gathered but when decomposing the smell is nauseating. The flavour is said to be delicious. The spores are round or oval  $8.9$  by  $7.8 \mu$  in diameter and are colourless. (Fig 80.)

*Amanita verna* (Frès 1871) Quélet, 1872 The Spring Amanita — This is apparently an early variant of the former species.

*Amanita virosa* (Frès 1836) Quélet 1872 — This is a distinct species with a conical crown which is viscous in wet weather but satin like in dry. It grows in moist woods. The margin of the crown is non striated but is lobulated and slightly indented. The stem is white cylindrical and provided with an ovoid bulb. The spores are white and round, and are  $7.8 \mu$  in diameter.

*A muscaria* (Pers.) The Fly Agaric — A striking and unmistakable fungus with scarlet cap, blood red or orange covered with white or yellowish warts. The stem is white or yellow tinged, with a bulbous base provided with prominent concentric scales. The flesh is white or yellowish. It grows in birch or coniferous woods, and is common from July to December. It is very poisonous but less so than *A phalloides*. An extract of the dried cap was used as a stimulant by many Siberian tribes and its sale was made a penal offence. The spores are white ovoid and spherical and  $9.11$  by  $8.9 \mu$  in diameter.

About nine other species of *Amanita* are known, but none are so poisonous as these four.

Leteulier has devised the following tests for edible and non-edible species —

The edible species give no precipitate in solution with dilute ammonia and with double iodide of mercury and potassium whereas the inedible fungi *A phalloides*, *A verna* and *A virosa* give a violet colour reaction with sulphuric acid, *A muscaria* gives a light brown colour. *A pantherina* gives a brown colour reaction. *A citrina* brownish green. *A vaginata* pale brown, and *A rubescens* faint purple. There are no colour reactions with *A junquillea* and *A spissa*.

The toxins of these fungi have been extensively studied. A viscous substance *viscosine* or mucilage of the toadstool is found principally in the epidermis of the crown. The species *A muscaria* contains a complex ammonia derivative, *muscarine*, the action of which closely resembles that of pilocarpine and a substance termed pilz atropin which stimulates the autonomic nervous system and produces an increased secretion from the various glands. *A phalloides* contains the toxic principles *amanita hæmolysin*, and *amanita toxin*, a glucoside. The hæmolysin is very active against the red blood corpuscles of the rabbit, guinea pig, dog, goat, fowl and pigeon as well as against those of man. These toxins are prepared by filtering an extract through a Chamberland

filter. When injected into a rabbit, they produce posterior paralysis and rapid death. Sheep are extremely susceptible to inoculation but are immune to the toxin when given it by the mouth.

**Pathology**—In the victims of mushroom poisoning subpericardial and subpleural hæmorrhages are seen and all the internal organs are congested. Intense fatty degeneration of the liver, resembling that due to phosphorus-poisoning has been observed and parenchymatous degenerative changes are found in the tubular epithelium of the kidneys. Severe and widespread damage is seen in the central nervous system and the brain is as a rule congested and œdematous. It is said that the characteristic spores of the fungi may be found in the fæces and adherent to the mucosa. There are minor differences in the general appearances of the spores of the different species. (Fig 81)

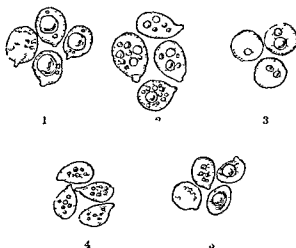


Fig 81.—Spores of poisonous fungi as they may appear in the fæces.

1 *A. pantherina* 8.9 × 7.8  $\mu$  2 *A. verna* 10.1 × 7.9  $\mu$  3 *A. crocea* 8 × 10  $\mu$   
4 *A. oreoidea* 10–15 × 5–6  $\mu$  5 *A. muscaria* 9–11 × 8–9  $\mu$ . (After Dujarric de la R. vère)

**Symptoms**—A number of clinical varieties of mushroom poisoning are recognized —

*Mycetismus gastro intestinalis*—In this type of poisoning violent nausea and vomiting with diarrhœa are the only symptoms. Recovery is usually rapid.

*Mycetismus cholericus*—In this type violent abdominal pains are followed by nausea and vomiting and usually by profuse diarrhœa. Nearly always severe hepatitis with jaundice is also present and toxic nephritis and anuria frequently occur. Poisoning of this type is caused by many varieties of *Amanita* but especially by *A. phalloides*.

*Mycetismus nervosus*—Severe gastro intestinal symptoms predominate at the onset and are soon accompanied by profuse salivation perspiration and lachrymation. Mental confusion and delirium occur usually in fatal cases. The fungi which produce this combination of symptoms are those

containing muscarine, that is *A. muscaria*, and some species belonging to the genera *Clitocybes* and *Inocybes*

*Mycetismus sanguinarius*—In this type of poisoning gastro intestinal symptoms occur at the onset, later there is rapid hæmolysis causing anæmia, jaundice, and hæmoglobinuria. The mortality is low

*Mycetismus cereбрalis*—In this form transient excitement with hallucinations and dilatation of the pupils is present. Collapse may occur. Recovery usually takes place

For practical purposes, cases of severe mushroom poisoning may be divided into two types—rapid and delayed. The rapid type occurs within three hours of ingestion of the fungi, this is usual in *A. muscaria* poisoning. In the delayed type, which results from ingestion of mushrooms of the *phalloides* group, the onset is delayed for six to fifteen hours or even more. abdominal pains are severe, nausea and vomiting extreme, and diarrhoea is also present

**Treatment.**—The most important step is to empty the stomach by lavage as soon as possible. If, in severe cases, this is not done in the first five to six hours, the patient is doomed. It must be remembered that atropine is the physiological antidote in *A. muscaria* poisoning, and should be given in large doses. To counteract the hæmolytic effect it is important to administer blood or saline intravenously

Diuretics in the form of potassium citrate should be administered freely, in order to eliminate as much toxin as possible. An antiserum to amanita toxin and amanita hæmolysein has been produced, but the results of its administration are inconclusive

A practical suggestion for treatment has recently been made by Mutch, who advises the administration of medicinal kaolin by the mouth, since the adsorption potency of kaolin for muscarine has been found to be at least 38 mg per gramme. Large doses of colloidal kaolin are indicated

## HENOCH'S AND OTHER FORMS OF PURPURA

Henoch's purpura also known as anaphylactoid purpura and toxic purpura, probably belongs to the same group as non thrombocytopenic purpura the so called purpura simplex, and peliosis rheumatica (Schoenlein's disease) all of which appear to be manifestations of the same pathological state. The term Henoch's purpura is usually restricted to those cases accompanied by urticaria, œdema, swollen joints, and various visceral manifestations. Undoubtedly, these states are allied to certain other allergic conditions, such as erythema nodosum, erythema multiforme, and angioneurotic œdema. It is thought that they result from an abnormal permeability of the capillary vessels which permits the escape of plasma and blood. The sensitizing agent is not, however, always the same

**Symptoms**—The characteristic symptoms are usually preceded by those of bodily disturbance, such as headache, malaise, and loss of appetite. In the very mild cases a pure purpuric eruption affects the

limbs in a symmetrical manner. This tendency to bleed is not confined to the skin, but may be intramuscular, periosteal or intravisceral. The gastro intestinal symptoms may take the form of colic, bilious vomiting or diarrhoea or they may be dysenteric in character, the discharges consisting of blood stained mucus. The abdominal wall may be rigid, when there may be difficulty in differentiating the condition from an intussusception or from the various forms of dysentery. The spleen may be palpable. Lesions occur in the genito urinary tract and albumin blood cells, and casts may be found in the urine. Nephritis is usually the most important complication. The results of examination of the blood are usually negative. There may be slight anaemia or mild leucocytosis. The blood platelets are normal or only slightly diminished and the coagulation and bleeding times are normal.

**Diagnosis**—The differential diagnosis has to be made from thrombocytopenic purpura, in which specific blood changes occur. Cases with intestinal lesions may closely simulate intussusception and may themselves be complicated by that condition or by peritoneal effusions. The differential diagnosis from the various forms of dysentery is not always an easy matter, as the case here cited indicates.

In May 1925 the author investigated the case of a schoolboy aged twelve who during a severe purpuric illness passed stools which were thought to be those of bacillary dysentery. At first he was thought to be suffering from German measles but ten days later he complained of abdominal pain and vomiting, this was followed in six days by a very profuse melæna which left him so collapsed that a blood transfusion had to be performed. For the next fourteen days intermittent intestinal hæmorrhages took place and eventually a generalized toxic arthritis supervened the toxæmia also manifesting itself in nephritis. For at least three weeks he continued to pass large quantities of albumin in the urine together with granular and hyaline casts. Later still there was intermittent pyrexia with the passage of dysenteric stools containing blood and mucus. A microscopic examination of the exudate revealed a cell picture like that of bacillary dysentery. No dysenteric organisms were however isolated and there were no other cases of dysentery in his school.

The diagnosis was Henoch's purpura.

In November, 1934, the author examined a second instance where bacillary dysentery had been tentatively diagnosed and which was certainly a case of arthritic purpura. This occurred in a lady of seventy years of age who had visited Capetown some seven months before the onset of the illness which commenced with an arthritis of the left knee. Later diarrhoea with blood and mucus supervened and finally purpuric spots appeared on both legs. The faeces resembled those of bacillary dysentery both macro- and microscopically. There was a leucocytosis of 20 000 and there were definite granular changes in the polymorphonuclears as well as the presence of myelocytes. The prognosis was grave and she died of generalized purpura some ten days later.

## Other Causes of Diarrhœa and Dysenteriform Symptoms

## CHAPTER XXVII

### CARCINOMA OF THE COLON AND RECTUM, POLYPOSIS, POLYPUS

#### CARCINOMA OF THE COLON

An exhaustive study of this very extensive subject is beyond the scope of this work, but since carcinoma of the large intestine or colon may at times give rise to the dysenteric syndrome—the passage of blood and mucus in the stool—it merits serious consideration in differential diagnosis. Methods of treatment will not be considered.

Carcinoma is by far the most common tumour found in this viscus, and, like carcinoma of the rectum, it appears to be becoming increasingly frequent. Possibly, owing to improved facilities in diagnosis, such as the development of radiological technique, it is more readily recognized than formerly. The most mobile terminal segments of the colon, the cæcum and sigmoid, are the parts most often attacked.

**Ætiology.**—The disease is more frequently found in males and occurs at any age, although it is usual to find it in those of fifty to sixty years of age, it may occur between the twentieth and thirtieth year. Its origin is obscure, but it may arise in benign adenomata; there is no proof, however, that all carcinomata arise from pre-existing polypi, though possibly multiple growths are due to malignant changes in multiple polypi.

**Pathology.**—Carcinomata of the colon are usually divided into 1, soft medullary adenocarcinoma, 2, scirrhotic carcinoma, or fibro-carcinoma, and 3, mucoid adenocarcinoma.

It has been remarked that the carcinomata of the right half of the colon are large ulcerating growths, and those of the left annular, hard and constricting. It is noteworthy also that medullary growths in the right side do not usually produce obstruction, because of the liquid nature of the fæces and the non-encircling character of the growth. Slow-growing carcinomata are more likely to produce chronic changes, including volvulus, inside the bowel. Eventually, ulceration and secondary infections take place, resulting in localized peritonitis and fistulous tracts. Perforation is more likely to take place at the flexures. Mucoid adenocarcinoma tends to spread widely over a considerable portion of the bowel, causing extensive thickening of the walls, and is likely therefore, to produce easily ascertainable and palpable tumours.

Local metastases usually occur in the lymph glands in any part of



the large intestine and it is rare to find metastases in the liver without implication of the lymphatic chain in the first instance. It is well known that metastases occur more frequently from carcinoma of the rectum than from any other segment of the bowel.

**Symptoms**—The symptomatology is so variable that it is difficult to describe it succinctly. Usually the onset of symptoms is insidious though rarely it may take place with alarming rapidity. As a rule there is diarrhoea with the passage of mucus and later of blood, there may be irregularity of the bowel movements, diarrhoea alternating with constipation. It is probably true that any profound change in the intestinal habits of an elderly person demands further investigation, chronic diarrhoea being more suggestive than chronic constipation.

Gastric symptoms commonly associated with colonic growths are chronic furred tongue, loss of appetite and dyspepsia. Borborygmi and visible peristalsis are considered to be early symptoms, but the latter can be recognized only in lean subjects. Pain is often an early symptom, but may be slight and unobtrusive, not unusually it is referred to the epigastrium. Tenesmus is probably present only when the growth is in the lower sigmoid or rectum, and as a rule the lower the growth, the more severe is the straining at stool.

Blood in the faeces may exist as such or mingled with mucus. When bright red it is probably derived from the lower part of the colon, below the splenic flexure, when its origin is higher up, it is dark and can be detected only by occult blood tests in patients who have been properly prepared with this object in view.

The duration of symptoms of carcinoma from all parts of the colon is estimated at from fifteen months to two years.

When carcinoma occurs in the right half of the colon it tends to produce a mild dyspepsia resembling chronic appendicitis or cholecystitis, with anaemia and progressive emaciation. A mass may then be accidentally discovered in the right iliac fossa.

A carcinoma in the transverse colon, owing to the mobility of this part of the bowel, has considerable latitude of movement and can alter its position without difficulty. Apparently carcinomata are more likely to cause obstruction in this situation than in other parts of the viscus.

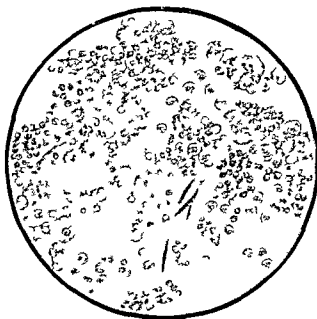
Growths in the left half of the colon tend to cause subacute symptoms of obstruction and do not give rise to such general systemic disturbances. Borborygmi, meteorism, and sometimes visible peristalsis are the more obvious signs. Progressive constipation is the rule. There is a tendency to perforation, and local abscess formation is common.

**Diagnosis**—The diagnosis of carcinoma of the bowel is by no means easy. It hinges largely upon differential considerations, and is, in fact, usually arrived at by a process of exclusion.

Although a combination of well ascertained signs and symptoms are suggestive, reliance has to be placed upon careful radiographic exam-

inations and it may therefore be said that as far as this disease is concerned the radiologist is more important than the pathologist. Radioscopic diagnosis is best effected by direct screening with palpation to detect filling defects and Fischer's double contrast method has proved invaluable in visualizing localized carcinomata in detail. The barium enema is more useful in detecting growths in any part of the colon than is a barium meal.

The importance of digital examination cannot be overestimated and sigmoidoscopy offers an invaluable method of recognizing growths



P J M B

Fig 82 — Appearance of cellular exudate and Charcot-Leyden crystals from a case of carcinoma of the rectum

within the range of that instrument. Diagnosis may be aided by microscopic examination of the faeces and a critical observation of the cellular exudate. In the author's experience shed epithelial cells are frequent while pus cells are comparatively scarce. Charcot-Leyden crystals are commonly encountered and blood cells tend to conglomerate in clumps (Fig 82). On the other hand the cell picture in the stool may not be in any way characteristic.

The chief difficulty in diagnosis is that carcinoma is so closely simulated by other tumours of the colon notably the hyperplastic form of amebiasis, hyperplastic tuberculosis (p 500), diverticulitis, segmental ulcerative colitis, polyposis, syphilis, actinomycosis and retrocaecal appendicular abscess. Occasionally also carcinoma of the

stomach and retroperitoneal growths, such as hypernephroma or lipoma, must be considered

## CARCINOMA OF THE RECTUM

Carcinoma occurs much more frequently in the rectum than in any other part of the intestinal tract with the exception of the stomach. It occurs much more often in men than in women, and most patients are between forty and seventy years of age, although young persons may also be affected. The duration of symptoms is usually shorter than in carcinoma of the colon, and averages less than one year. The average duration of symptoms in cases treated at the Mayo Clinic was about eleven months, while in the large series of 1,234 analysed by the Ministry of Health it was just over thirteen months.

**Ætiology.**—In this situation also it is difficult to surmise the starting point of carcinoma except to state that it is apt to arise in a polyp. Constipation does not appear to be a predisposing factor.

**Pathology.**—Carcinomata of the rectum develop from the glands of Lieberkuhn, and are usually adenocarcinomata. Those originating in the anal canal are true squamous celled growths. Adenocarcinomata of the rectum tend to undergo mucoid or colloid degeneration. Metastases from rectal neoplasms occur, especially in the liver, generally in proportion to the degree of malignancy.

**Symptoms.**—Rarely do the symptoms such a growth may evoke justify the suspicion of rectal carcinoma for indeed they may be those produced by any other rectal condition. It is obviously of paramount importance that its existence should be recognized as early as possible, so that remedial steps may be undertaken.

The most constant outward sign is bleeding, which varies from actual hæmorrhage to simple streaking of the stool at the end of defæcation. At other times blood and mucus may be passed at the end of defæcation, or may be intermingled with the fæces as in amoebic dysentery, these are the cases which it is sometimes so difficult to differentiate from other dysenteric diseases. As a general rule, carcinoma of the rectum is not associated with such profound anæmia as is carcinoma of the colon. Usually the development of such a growth in the rectum or pelvic colon is associated with some change in the intestinal habits of the patient, or some signs of irritability. Increase of meteorism is one danger signal, sudden attacks of constipation alternating with diarrhoea constitute another. Sometimes the stools are ribboned and otherwise deformed, but this only occurs when a very considerable degree of stricture is present.

Pain appears to be a most variable symptom, and is present usually when the neoplasm has spread to surrounding structures, and has involved some nerve, in the rectal mucosa itself pain sensation is absent. Pains in the sacrum and shooting pains in the hips and thighs

are referable to the metastases. Loss of weight is usually quite untrustworthy in the earlier stages.

It has been generally remarked that growths in the rectal ampulla produce symptoms only when they have attained very considerable size, this is probably due to the space in which they can expand. When, however, such a growth ulcerates the feces become mingled with necrotic shreds, pus, mucus and blood, giving out an offensive odour, considered to be characteristic of carcinoma. When the growth has touched laterally adjacent organs, such as the urinary bladder, uterus, or sacrum these become involved and symptoms are produced referable to these structures.

**Diagnosis**—The diagnosis of rectal carcinoma is often established by digital examination, but many of the lesions are situated beyond the reach of the index finger—some can be reached better by bimanual examination. Usually the only satisfactory measure is the use of either proctoscope or sigmoidoscope. The appearance of a carcinomatous growth in the rectum—the typical cauliflower growth—is so characteristic that it is hardly likely to be mistaken for anything else. The sigmoidoscopic appearances have to be distinguished from polyposis, amœbic dysentery, ulcerative colitis, tubercular disease, and many of the other pathological states described in this book, but there appears to be no reason why a mistake in diagnosis should arise if the various methods described in Chapter I are followed and microscopic examinations of the exudate are undertaken. Certainly the sigmoidoscopic picture produced by amœbiasis is so characteristic as not to admit of any reasonable element of doubt.

Biopsy methods should, of course, always be used whenever possible, portions of the growth being removed for microscopic section. One must be careful not to be misled by the presence of the *E. histolytica* in the feces, because this does not preclude the co-existence of carcinoma. The author encountered two cases in which the patient was obviously suffering from amœbic dysentery when at the same time a carcinomatous ulcer was present in the rectum. A large indurated rectal ulcer due to amœbic ulceration is also met with occasionally, and may be mistaken for carcinoma. Two such cases have been seen and the correct diagnosis was made by demonstrating active *E. histolytica* in scrapings from the ulcerated surface (see p. 174).

Much useful information is to be gained from a microscopic examination of the exudate. The author has found that, besides shed epithelial cells, these blood and mucus stools contain cellular debris, clumps of red blood corpuscles and, very often, Charcot-Leyden crystals. It should be noted that these crystals are often found in association with malignant growths, and the diagnostician is warned against the premature assumption that, because these crystals are present, the case is necessarily one of amœbiasis. An instance of such a mistaken diagnosis may be mentioned—

A naval officer 46 years old stationed in Malta had been treated for two and a half years for chronic amœbiasis solely on account of the presence of Charcot Leyden crystals in the faeces together with blood and mucus. A digital examination of the rectum revealed a large fungating malignant growth necessitating an abdomino perineal operation (Fig 83)

Radioscopic methods are of little avail in diagnosis unless the filling of the rectal ampulla is actually visualized on the screen. Obviously



Fig 83 —Carcinoma of rectum showing lymphatic spread  
(Preparation by Dr. Cuervo Lutz)

there is no necessity for this method to be employed when the growths themselves can actually be seen

### POLYPOSIS INTESTINI

**Synonym** —Multiple adenomata of the colon

Polyposis indicates diffuse adenomatosis of the large intestine. The term polypoidosis is however preferred by Rankin, Bergen and Bue in their textbook as indicating more satisfactorily an adenomatous hyperplasia (polyadenoma).

Polyposis intestini has to be distinguished from the polypoid formations found in association with hyperplastic tuberculosis, bilharziasis,

chronic bacillary dysentery, and often with chronic ulcerative colitis. Pierre Augier (1932), who has given the most complete account of the condition, considers that it is identical with colitis polyposa (Virchow, 1860), polyadenoma tractus intestinalis (Skilasowski, 1881), polyposis intestinalis adenomatosa (Hauser, 1895), and polyposis intestini (Ziegler, 1903).

Another important monograph on this disease is by H. Tonnesen of Copenhagen (1931) who, in a review of forty cases culled from the whole of Denmark, has shown that polyposis intestini is of the same nature as the similar polypi found occasionally in the stomach.

These multiple adenomata are really true neoplasms of congenital origin, are usually familial (as Cuthbert Dukes has so ably shown), and are known to undergo malignant changes in 40 to 50 per cent of cases.

**Ætiology.**—Polyposis is a disease of youth or early middle age. Doering recounts the following age incidence in forty cases —

1-10 years,	2 cases
10-20     "	10     "
20-30     "	10     "
30-40     "	13     "
40-50     "	2     "
50-60     "	2     "
60-70     "	1 case

Schottler's review of ninety-eight cases gives much the same proportions.

Cohnheim originally considered that these tumours developed from some congenital malformation, and from this idea has gradually developed the modern theory that the tumours arise from certain embryonic cells excluded during foetal life from their connexion with other epithelial cells.

The distinguishing features of polypi secondary to inflammatory or irritative lesions are the irregular shape of the tags of mucous membrane and the fact that they are usually attached to the line where the blood vessels pierce the intestinal wall. In true polyposis intestini the polypi, which may be either sessile or pedunculated, preserve a smooth and rounded outline and are scattered evenly over the whole mucous membrane. The charts published by Cuthbert Dukes, giving the pedigrees of thirteen families, notably the three studied by Lockhart-Mummery, show that polyposis intestini is indubitably a hereditary disease, transmitted by both males and females, the inheritance being acquired on a Mendelian basis which can be traced through several generations\*. This curious fact appears to have been recognized first in 1892 by Harrison Cripps, and it has since been commented upon by many writers.

The disease is certainly more common in men than in women. This fact was specially noted by Doering who, among his forty-two cases,

\* See also Tonnesen's series.

found twenty five in men and seventeen in women. Jonnesen gives a much higher proportion for he finds it to be eight times more common in males than in females.

Polyposis is certainly a rare disease and that it has become more generally recognized during recent years is probably due to the increased use of the sigmoidoscope as an aid to diagnosis.

**Pathology**—The individual adenomata may vary from small raised elevations a few millimetres in diameter to large polynucleated tumours which as pointed out by P. Augier may be extensive enough to cause intussusception and obstruction (Fig 84). Usually the polypi



Fig 84.—Polyposis intestinalis of the rectum

(From a specimen of Malakouti by permission of the Cylichre)

are pedunculated the elevation of the thickened mucosa resulting in the formation of a pedicle but they may be sessile and sometimes both varieties are found intermingled. Occasionally one or more segments of the colon is specially affected but as a rule the tumours are disseminated throughout its whole length (Fig 85).

In histological characters they are identical with the similar polyps found in the stomach and small intestine. The individual tumour has a basis derived from the fibrous tissue of the submucosa and is lined with cylindrical deep staining goblet cells. Retention cysts are common.

Though many individual polypi retain their inflammatory character, there is a tendency to malignant changes. In fact, it is probable that, should the patient live long enough, carcinoma of the intestine is bound to supervene. Doering has reviewed the cause of death in thirty six cases of polyposis and found that in twenty one it was carcinoma, other fatal causes were intussusception, hæmorrhage, peritonitis and inanition. This tendency to carcinomatosis has undoubtedly given rise to the idea that carcinoma of the colon is hereditary.

By making serial sections of pedunculated polypi, Rankin, Barger

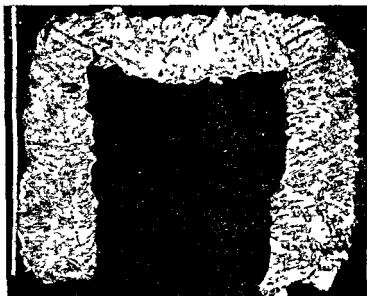


Fig 85 —Polyposis of the large intestine of familial origin

(From a specimen in St Mark's Hospital by permission of Sir C Gordon Watson)

and Buse have shown that the carcinomatous changes initiate from adenocarcinomata situated in the centre of the adenomatous portion of the polypi (Fig 86). It appears that the development of carcinoma in the polypus depends upon the rate at which the tumour is forced to grow when acted upon by the peristalsis of the intestines. The peristaltic action is violent enough to cause actual avulsion of individual polypi and numerous cases of intussusception have been recorded from this cause.

Tonnesen, in a review of the microscopic pathology of all polypi described in the intestinal tract divides them into three groups: those derived (a) from the epithelium (b) from connective tissues, and (c) from the muscle layers. The first is by far the most frequent. In



the last two groups are fibroma, enchondroma, lipoma, myxoma, and sarcoma. The microscopic structure of individual growths in true polyposis suggests that they are adenomata with a special tendency to malignant changes.

**Symptoms** —The severity of the symptoms naturally depends to a great extent upon the area of the bowel involved. The outstanding symptoms are abdominal pain, diarrhoea, and dysenteric blood and mucus stools. The diarrhoea varies in intensity, some patients having



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Fig. 86 — Microscopic section of polyposis showing early carcinomatous changes originating at the base. (Author's case.)

but a mild looseness with two or three stools daily, others choleraic diarrhoea with thirty or more watery movements. Usually diarrhoea alternates with constipation as in the true carcinomatosis. Occasionally nausea, vomiting, and anorexia are met with, and loss of weight and progressive weakness are usual. In some cases large rectal hæmorrhages occur suddenly; this may be the first sign of the malady and causes a great change in the general appearance of the patient. Occasionally polypoid masses are extruded from the anus.

Pain ranges from indefinite abdominal distress to intermittent cramp and colicky pains which may persist for days or even weeks. In between attacks there is a sense of fullness over the whole colon with vague discomfort which may be caused by increased tension

Intestinal obstruction occasionally occurs, and may be due to occlusion of the lumen by direct growth of the polypi, malignant changes in the polypi, or intussusception

P Augier has drawn attention to the association of polyposis with "Hippocratismes digitales," or incurvature of the nails with hypertrophy of the terminal digital phalanx. This has to be distinguished from an early stage of hypertrophic pulmonary osteoarthropathy. Polyposis of the bowel in young people is often associated with infantilism. The rectal symptom in these cases is usually tenesmus, as in other forms of rectal disease, or there may only be a sense of irritation. Occasionally a large rectal hæmorrhage occurs.

**Diagnosis**—In making a diagnosis, suggestive features are the absence of any ascertainable ætiological agent, the age of the patient (usually under thirty), and the familial character, if a history is obtainable.

When the polypi are crowded into the rectum, as is usually the case, they may easily be felt by digital examination, but diagnosis is best made by proctoscopy or sigmoidoscopy. The appearance of the polypi is characteristic. Augier states that eighty to one hundred may be revealed in the tract explored by the sigmoidoscope. They vary in colour from pale rose to deep red and a considerable degree of bleeding and oozing is generally encountered, this serves to distinguish them from simple polypi. The polypi may be removed through the instrument, and their microscopic structure ascertained.

In making a diagnosis due regard must be had to the condition of pseudo polyposis in association with chronic ulcerative colitis, and also occasionally with tuberculosis of the large intestine, and in this connexion the absence of visible pus in the stools is useful. It has also to be distinguished from *gastro intestinal pseudo leucæmia* a primary lymphoid hyperplasia described by A. D. Fraser of the Bristol Royal Infirmary.

Radioscopic methods are of value. X rays after a barium enema, especially if applied by Fischer's double contrast method, show most distinctly the presence and distribution of the polypi. Fischer's contrast method consists of cleansing the bowel with hot water enemata giving an opaque enema which is immediately evacuated as completely as possible, and then insufflating the colon with air until the cæcum is reached, whereupon successive stereoscopic pictures are taken.

Polyposis is usually associated with secondary blood changes—mainly a moderate or severe anæmia, depending upon the blood loss. There is usually a leucocytosis of 13,000, and sometimes, as in other forms of severe bowel disease, a marked eosinophilia.

The following is the clinical record of a typical case which illustrates the difficulties encountered in diagnosis.—

A farmer, aged thirty, entered hospital in February, 1933. He had come straight from Southern Rhodesia where he had been working for one year. There he was at first considered to be suffering from amoebic dysentery, for he

had attacks of diarrhoea with blood and mucus in the stools alternating with constipation. On admission he was passing about six dysenteric stools a day. Microscopical examination of the cellular exudate gave a picture resembling that of amoebic dysentery, while sigmoidoscopy revealed, about 5 cm. from the anus, numerous sessile polypi with a granular, easily traumatized surface.

Three of the polypi were removed for microscopical section, and it was then seen that the whole of the rectum and sigmoid colon were studded with similar excrescences. On section the polypi were found to consist of typical adenomatous tissue, but at the base malignant cell nests had commenced to form (Fig 86). Later he was re-admitted for an exploratory operation but when examined under an anæsthetic masses were found by rectal and abdominal examination which showed that the malignant changes had already progressed and dissemination had already taken place. The patient refused further operative procedure and died a month afterwards. In his case no evidence of hereditary disposition could be obtained.

The author has notes of four other cases, all in men, who were referred as suspected cases of intestinal amœbiasis, but none of them was as striking as the above, and in no others could the process of malignancy be so intimately observed.

*Duration of the disease*—Polyposis is usually a long drawn out, chronic, painful malady. In H. Tønnesen's series of forty cases he recorded the duration as being under one year, six one to five years, fourteen, five to ten years, nine ten to thirty years, eleven times. The progress of the disease appears to bear no definite relation to the age of the patient.

*Treatment*—Treatment of this very severe disease is undoubtedly unsatisfactory. When it is limited to one segment of the bowel, resection of the involved area, or transperitoneal colectomy, has been performed. When, however, the process involves the entire lumen of the bowel, colectomy is indicated, but this is a very formidable procedure, involving great risk. Tønnesen has summarized the results of total colectomy in a table giving the end results of operative measures. Out of twenty nine cases twelve died. In the remaining seventeen the results were excellent. The primary operative mortality therefore stands at about 41 per cent, this including a case which died shortly afterwards (Table XVI).

As palliative measures, enterostomy, appendicostomy, colostomy, and ileostomy have all been advocated. Ileostomy at least puts the colon at rest and may give relief, provided that malignant changes have not already set in.

The results of radium therapy have so far been inconclusive. Bleeding from the bowel may be to some extent controlled by enemata of 1 per cent tannic acid or applications of Congo red as a hæmostatic.

TABLE XVI

<i>Authority</i>	<i>Cases</i>	<i>Result</i>	<i>Period of observation</i>
Bardenhauser	1	dead	—
Borebus	1	good	10 years
Bratrud	1	good	1 year
Carrol	1	good	—
Coffey	3	{ 1 good 2 dead	1½ years
Czermade	1	dead	—
Brentano	1	improved	—
Hausser	2	dead	—
Karajun	1	good	—
Landner	1	good	4 years
Lohenthal	1	good	—
Lockhart Mummery	1	good	5 years
Morkowitz	1	good	—
Quénu	1	dead	—
Rotter	1	good	lived 2½ years
Piederer	1	good	died shortly afterwards
Schmieden	2	{ 1 good 1 dead	—
Soper	1	good	—
Steinthal	1	good	—
Struthers	5	{ 2 good 3 dead	6 years
Willing	1	dead	—

## POLYPUS

**Synonyms** — Simple adenoma, pedunculated adenoma

**Ætiology** — Polypus is the most common benign tumour of the rectum and it is stated by F C Yeomans that two thirds of all polypi of the intestinal tract occur in this locality. It arises from the epithelium of the glands of the mucosa, generally in the lower and more easily accessible part of the rectum. At first an adenoma is sessile but owing to the constant traction set up on defæcation, it soon becomes pedunculated—so much so that polypi may be the exciting cause of local intussusception of the mucosa.

According to A J Walton the term polypus denotes the actual configuration of the growth and refers to a pedunculated tumour whose microscopical appearance is that of an adenoma.

These simple adenomatous structures may occur singly or in groups. They are much more frequently found in children than in adults, but may arise at any age. The oldest patient in the author's series was sixty seven, at which age they are to be regarded with suspicion on account of the liability to carcinomatous changes. They often occur in "chaplet" form, as a ring encircling the bowel, and they tend to recur at the same site after surgical removal or cautery. Though usually situated within the rectal ampulla large pedunculated polypi may protrude from the rectum.

Lockhart-Mummery considers that the natural evolution of all rectal adenomata is to become eventually cancerous. From continued observation, he believes that the following stages are noted in sequence. At first there occur localized patches of hyperplasia affecting an extensive area of the bowel, then a crop of sessile adenomata appears scattered over the same area, lastly, carcinomatous changes develop either in one of the pre-existing adenomata or in the neighbouring epithelium. The adenomata, however, may reach a large size without undergoing malignant changes.

These polypi are epithelial tumours consisting of an excessive development of the normal glandular elements of the mucosa. The hypertrophy remains confined to the epithelial layer. The simplest form of polypus is attached to the bowel wall by a long narrow pedicle, and is known as "soft rectal polypus". Sometimes it is branching and tree like, and it is then known as a 'villous tumour', these usually exude a mucoid secretion often tinged with blood. When viewed through the proctoscope these polypi appear as delicate pink tendrils, and have to be distinguished from malignant growths.

**Symptoms.**—The presence of a polypus in the rectum, or indeed in any portion of the large intestine, produces considerable irritation and increased peristalsis. When solitary polypi are situated high up in the colon, in the sigmoid, or beyond the range of the sigmoidoscope, it is obviously very difficult to associate the patient's variable symptoms with their presence. When they are in the rectum he complains of constant tenesmus, diarrhoea, and the intermittent passage of blood and mucus in the stools. Often there is a smart and not inconsiderable hemorrhage which, as in hemorrhoids, may appear at the end of evacuation. Children with polypi often scream with pain on passing stool, though they are free from symptoms at other times. This alone should draw attention to the condition, and, in the absence of any constitutional symptoms, should serve as a signpost in the differential diagnosis from the dysenteries.

Patients with polypi are usually full blooded and of good complexion, and give the impression of being in good health.

**Diagnosis.**—The diagnosis of polypus is arrived at by a consideration of the history and course of the complaint, and by the presence of pain, discomfort, and tenesmus in a patient who is otherwise well. Very often polypi can be palpated by a simple digital examination of the rectum, or, more satisfactorily, they can be visualized by the proctoscope or sigmoidoscope and their characters easily ascertained. In case of doubt, a portion of the polyp should be removed by biopsy for microscopic examination. In every case a barium enema should be employed to reveal the possible existence of other polypi situated higher up the bowel.

• Some indication of the nature of the complaint may be obtained by a microscopic examination of the rectal discharge. In blood and mucus accompanying a polypus, there occur, usually, large numbers of

red blood cells, and very often columnar epithelial cells, but there are no inflammatory pus cells such as are visible in other irritative lesions. The author has been able on several occasions to arrive at a diagnosis by these simple means.

**Treatment**—All polypi of the rectum should be removed as soon as possible. The older the patient the more likely are malignant changes to occur. Small polypi and adenomata can be removed through a speculum or proctoscope, either being snared or snipped away with forceps. Sometimes they can be ligatured. When situated higher up in the rectum they can be twisted off by crocodile forceps, and the bases subsequently cauterized.

*Analysis of the Author's series of fourteen cases of adenomatous polypus of the rectum*

All these cases were originally referred as suffering from some kind of dysenteric disturbance and the chief complaint was usually abdominal pain or the passage of blood and mucus, both or separately in the faeces. All the patients were males, their ages varying from five years to sixty seven and all were tropical residents.

The chief point of differentiation from dysentery was the benign character of the symptoms and the history of occasional passage of blood and mucus. When blood was present in the faeces it was noted to be brighter in colour and more abundant than that usually found associated with amœbic dysentery. Microscopic examination of these specimens shows comparative scarcity of pus and inflammatory cells and abundance of red blood cells. An additional temptation to classify tropical cases as amœbic dysentery lay in the occasional presence of Charcot Leyden crystals.

In the majority of these cases the polypi were multiple—in only two was a single polypus revealed—and situated 4 to 18 cm from the anus. All proved on section to be benign adenomata.

The following cases are cited as representative —

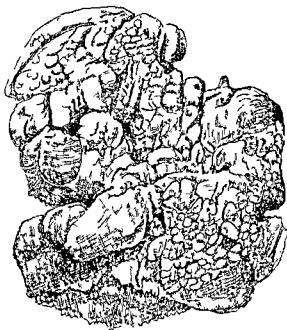
The first was that of a boy of six who was sent from Northern Rhodesia as a case of incurable amœbic dysentery of 2½ years duration. There had been considerable hæmorrhage and he was anæmic as the result. The diagnosis of probable polypus was made from a microscopic examination of the faeces. A small polypus the size of a cherry was removed 10 cm from the anus.

A man of twenty nine from India had been treated off and on for eight years for presumed amœbic dysentery. His chief symptoms were diarrhoea and epigastric and abdominal pain and discomfort. A pedunculated simple polypus 15 cm from the anus was removed.

The third case was that of a medical man aged thirty seven from China. He was thought to have an infection of both amœbic and bacillary dysentery his symptoms including the intermittent passage of blood and mucus in the stools with Charcot Leyden crystals. Pedunculated adenomatous polypi were removed 12 cm from the anus.

The fourth case exemplifies the symptoms caused by a branched adenomatous polypus of large dimensions. A well preserved man of sixty seven gave a well defined history of colitis of four years standing which had been unquestioningly regarded as mucous colitis. He described the mucus as

passing in strings and masses and leaking through the anus sometimes eight to twenty times a day. Directly he took any form of exercise the discharge of mucus and the desire to defæcate increased. Dieting in any form appeared to have little effect. The fecal specimen was watery and contained mostly mucous cells. The diagnosis of polypus was made in the first instance by rectal examination an adenomatous mass being felt 10 cm. from the anus. This was confirmed by sigmoidoscopy and finally a large cauliflower shaped



P. H. M. B.

Fig. 87—Adenomatous polypi removed from the rectum. The mass resembles a cauliflower in shape and appearance. (*Half nat. size*)

polypus 3 inches in diameter was removed at operation by T. P. Hulner (Fig. 87). On section it proved to be a simple adenoma. There was a small recurrence at the site four years later which was also removed. The patient's general health has since remained excellent.

The main interest of this case was the resemblance to mucous colitis, the absence of blood in the feces, and the benign nature of the symptoms produced in view of the size of the tumour.

## CHAPTER XXVIII

### ACTINOMYCOSIS, TUBERCULOSIS AND SYPHILIS OF THE LARGE INTESTINE

#### ACTINOMYCOSIS OF THE LARGE INTESTINE

ACTINOMYCOSIS is an infection by a fungus of the genus *Actinomyces* (*Streptothrix actinomyces*). It is characterized by a tendency to form abscesses sinuses and granulation tissue often it invades the surrounding tissue.

Actinomycosis of the large intestine is probably more prevalent than is usually believed. It commonly commences in the ileo cæcal region and it is clear that the point of origin is a diseased appendix. It is well known that ruptured appendices may heal up and leave little trace behind and thus actinomycosis spores may escape into the abdominal cavity. When the actinomycoma commences to grow it is always subperitoneal and advances upwards inexorably. The hard swellings sooner or later soften and the semi fluid material finds its way to the surface of the body and produces red fluctuating areas. From these abscesses actinomycotic pus may be obtained. In the transverse colon the lesions tend to develop external to the gut rather than in the gut wall and are apt to be mistaken for carcinoma.

Secondary rectal actinomycosis is the form in which the primary focus of the disease is in some other viscus whence it extends to the rectum. Primary rectal actinomycosis presents a more definite picture. Infection takes place high up in the rectal canal and spreads in the loose cellular tissue towards the iliac fossa and hypogastrium. Z. Cope (1938) has described the sigmoidoscopic appearances of a case under the care of Gordon Taylor. There is irregularity and puckering which is somewhat comparable to that observed in skin lesions and a few yellow submucous actinomycotic granules are visible. In the case described there was stenosis of the rectum 4 cm. from the anal orifice. Actinomycosis of the stomach and small intestine are pathological curiosities.

**Pathology**—When the fungi occur in colonies they form masses which are visible to the naked eye having a yellowish or sulphur like appearance. In each colony there are rays like a group of clubs which emanate from a central mass. There is some evidence that the infecting fungus is derived from a carious tooth or it may be from the tonsils. In the mouth the disease often develops after extraction of teeth.

Actinomycosis is a most destructive disease and in animals it pene-



trates the interstices of bones with the same ease with which it invades muscles

**Symptoms**—In abdominal actinomycosis, acute, chronic, and pyæmic forms occur. The chronic form is the only one which can be diagnosed with certainty, but the distinction from malignant disease and tuberculosis is extremely difficult, and becomes increasingly so until sinuses are formed, which discharge the characteristic sanious pus containing sulphur granules. It is from these granules that the ray fungus can be isolated disclosing the causative agent.

The acute type of actinomycosis of the cæcum is frequently mistaken for acute appendicitis. occasionally the ray fungus has been isolated from the pus in the lumen of the appendix, so that on clinical grounds it is not possible to distinguish the condition from septic appendicitis.

A case of streptothricul ulceration of the colon with portal and systemic pyæmia has been described by N. H. Fairley and F. P. Mackie.

This patient who came from China was in hospital in December 1934. The irregular fever with rigors associated with night sweats and an enlarged liver suggested at first hepatic abscess, a dense opacity in the liver area (shown by X rays) supporting this diagnosis. An exploratory laparotomy was performed and subsequently the patient died. At autopsy numerous necrotic and suppurating areas were found in the liver. The sigmoid flexure and the descending colon were matted together by adhesions and punched out ulcers were demonstrated in the mucosa. In sections there were areas of tissue necrosis in which delicate filaments of *Streptothrix* mycelium were found ramifying. The organism was found to be a *Streptothrix* allied to *Actinomyces mairiae* the pathogenic agent of Madura foot.

An almost identical case is described by Rankin, Bergen and Bue. In this case appendicitis was first diagnosed and the appendix was removed. Subsequently symptoms suggestive of hepatic abscess supervened. Actinomycotic disease of the large intestines may be associated with chronic diarrhoea and occasionally with dysentery like stools.

**Diagnosis**—Diagnosis is established by finding the yellowish green sulphur granules in which when crushed on a glass slide the characteristic clubs may be recognized. They may be confused with inspissated pus.

Chronic tumefaction due to actinomycosis unaccompanied by the formation of sinuses may be confused primarily with hyperplastic tuberculosis or with intestinal or retroperitoneal sarcoma.

**Treatment**—Actinomycosis may be successfully treated by medical, surgical or radiological measures.

Until recently medical treatment consisted of the administration of massive doses of a saturated solution of potassium iodide 50 to 200 grains three times a day. Usually radium and X ray therapy were given concurrently with the potassium iodide.

A surprising development has been the recently discovered action of the sulphonamides upon this fungous disease. These drugs must be

given in massive doses. The first success was reported by O. Walker (1938), others by E. M. Miller and E. H. Fell (1939), W. H. Ogilvie, G. C. Dorling and N. L. Eckhoff (1940). The latter treated five severe abdominal infections, four recovered completely and one died. In one case later operation showed that all evidence of the disease had disappeared. Sulphapyridine appears the drug of choice, in doses of 6 gm., daily for four days—a total of 24 gm.—succeeded later by a course of 38 gm. E. M. Miller and E. H. Fell's case was in a boy of 11 who had 1.9 gm. for seven days and subsequently increased in weight 100 lbs. in one and a half years.

The success of bowel resection in actinomycosis depends on the possibility of completely removing the infected portions.

### TUBERCULOSIS OF THE LARGE INTESTINE

It is generally held that tuberculous infection of the colon is rare as compared with the incidence of this disease in the small intestine. Amongst 230 adult patients who died of tuberculosis, Goldberg and Smithies found intestinal tuberculous lesions in over 80 per cent. In 1911 Park and Krumweide, reviewing fifty-five cases of abdominal tuberculosis, found that in children under five years of age, the bovine type of bacillus was responsible for the infection in 59 per cent. of cases, in those ranging from five to sixteen years of age, it was the causative agent in 46 per cent., but in patients of sixteen years, or over, it accounted for only 22 per cent. It therefore appears that the human type of bacillus is the chief factor in the intestinal tuberculosis of adults.

Intestinal tuberculosis is a disease of relatively young people. Thus Brown and Gaither found the average age to be about thirty-five. Primary tuberculosis of the intestinal canal is more commonly found in children than in adults. The proportion of sexes is about equal. Probably the incidence is really greater than has been recognized in the past, for it is fairly certain that a number of tuberculous cases have been diagnosed as actinomycosis, sarcoma, and even carcinoma.

In recent years medical interest has centred upon the hyperplastic form of tuberculosis, which mainly affects the caecum and tends to cause considerable difficulty in differential diagnosis.

**Ætiology**—It is generally held that tubercle bacilli gain access to the intestinal canal by being swallowed with the sputum in cases with extensive cavitation of the lungs. It is probable, however, that the intestinal lesions are the result more of the lowered resistance of the patient than of the large numbers of bacilli ingested.

The terminal ileum and caecum are the portions most usually attacked (85 per cent. of cases, according to P. W. Brown, Laurason and H. L. Sampson). In the remaining 15 per cent. the lesions are found scattered throughout the extent of the colon. Primary tuberculosis of the large intestine appears to be considerably rarer than infection secondary to pulmonary lesions.

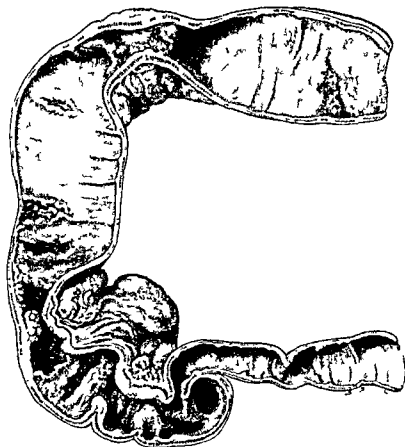


Fig 88 —Tuberculosis of cæcum and ascending colon showing hypertrophic type of lesion and several shallow girdle ulcers

(By permission of Dr. C. Lord Faxon)

Previous damage to the intestinal mucosa from dysenteric infection definitely predisposes to tuberculous disease. This is probably the reason for the relative frequency of primary tuberculous infection of the large intestine in tropical practice.

**Pathology**—In the ulcerative type of lesion which is the one usually encountered the process is largely destructive. The generally accepted view is that the bacilli pass through the mucous membrane of the intestine without producing any obvious injury and eventually lodge in the submucous lymphoid tissue (Fig 88).

The tuberculous ulcers possess certain characteristics which render their recognition relatively easy. They occur at right angles to the long axis of the bowel and have a tendency to become annular in shape. As a rule the more recent ulcers have diffusely caseous bases. *The edges are scalloped and irregular the margins raised and undermined.* Pearly tubercles are usually visible on the peritoneal surface. When the infection is sufficiently severe the mesenteric glands are involved as well and adhesions to adjacent loops of bowel and to omentum and parietal peritoneum are commonly encountered. Rarely pseudo-polyposis resembling that of ulcerative colitis is produced (A. I. Taylor Bristol General Hospital).

In the *hyperplastic* type of tuberculosis the process may extend along the intestine for varying distances but is usually confined to one segment. The tumour produced is hard dense and usually red. The tubercle bacilli infiltrating the bowel wall produce fibrous hyperplasia rather than the caseation encountered in the ulcerative form. The bacilli are very sparsely distributed being demonstrated with difficulty.

Gross or hyperplastic tuberculosis of the rectum consists of massive involvement of part or even the whole of the rectal canal the wall of the bowel being infiltrated stiff and rigid.

The hyperplastic type does not appear to be so commonly associated with pulmonary lesions as does the ulcerative form and many observers consider that the tumour or tuberculoma is often due to a primary infection.

**Ulcerative type.** *Symptoms*—It is necessary especially in the ulcerative type that the disease should be recognized early in order that appropriate treatment may be instituted as soon as possible. In persons who are known to have tuberculosis recognition is comparatively easy. It must of course be borne in mind that diarrhoea occurs quite commonly in advanced pulmonary tuberculosis without any recognizable intestinal lesion. It may alternate with constipation. During an attack of diarrhoea the stools are usually profuse thin watery and very offensive while blood though not obvious can usually be detected by chemical tests.

Occasionally dysenteric discharges with blood and mucus are passed. Hence the importance of the subject in a differential diagnosis of the dysenteries. Cases of ulcerative tuberculosis undoubtedly do occur in which on account of the accompanying pyrexia the distress of the patient the exhaustion and toxæmia and mainly the blood and mucus discharges idiopathic ulcerative colitis is mimicked very closely. Gross intestinal hæmorrhage is rare.

The physical examination of the patient may not be very helpful. As a rule the abdomen gives a doughy feeling massive infiltration of the colon may actually be felt or the outline of the large intestine may appear as an elastic cord. Enlarged mesenteric glands may be palpable. On the other hand in the author's series of cases the majority presented no physical signs in the abdomen at all.

**Diagnosis**—At the outset it can be stated that there is no single clinical laboratory test for intestinal tuberculosis which has not its shortcomings. The final diagnosis rests entirely on the demonstration of tubercle bacilli in the faeces or in preparations made from the intestinal lesions by proctoscopy or sigmoidoscopy. This is by no means always easy.

There are cases in which the acid fast bacilli are so numerous in the discharges that their recognition is a simple matter in ordinary fixed smear preparations of the faeces. There are others again in which the organisms are so scanty that they can be demonstrated solely by concentration methods. The demonstration of acid and alcohol fast organisms in the faeces in a case which is suspicious from the clinical aspect may be taken as a further indication that the case is tuberculous in origin. It is however not quite such an easy matter to decide whether all acid fast bacilli in the faeces are necessarily tubercle bacilli (See p. 569).

Proctoscopic examinations should always be undertaken in intestinal ulcerative tuberculosis but it is admittedly extremely difficult to make a diagnosis in every case by this examination alone. Where ulcers can be visualized they must be scraped and microscopical preparations made—a positive diagnosis can then be made by demonstration of acid fast bacilli in the lesions. The ulcers are fairly distinctive in appearance with undermined pearly edges and grey bases. In patients who have recognized pulmonary tuberculosis the existence of any ulcerative lesion in the rectum is very suggestive.

Some forms of carcinoma may resemble massive tuberculosis of the rectum and in tropical practice it will be found that some small tuberculous ulcers closely resemble those produced by *Entamoeba histolytica*.

Tuberculosis of the ulcerative type has also to be differentiated from the many different forms of dysentery and colitis.

Tuberculosis of the anal margin—a very rare phenomenon—is a condition in which fissures or other lesions not of malignant or syphilitic origin are present and refuse to heal up in spite of operative measures. Fistula is also a complication and occasionally ischio-rectal abscess.

**Hyperplastic form** *Symptoms*—The hyperplastic form is more difficult to recognize in the early stages than is the ulcerative type. The problem is complicated by the fact that gross lesions of the caecum and other parts of the colon may be present for long periods without producing symptoms. Pain is by no means constant and varies in severity from slight discomfort to an intense degree of pain such as is more usually associated with intestinal obstruction. It may be intermittent and colicky and is usually intensified by pressure over the affected area or by a change in position such as is entailed in walking about. Involvement of the mesenteric glands may occasionally produce some abdominal distress. Nausea and vomiting may complicate the clinical picture.

**Diagnosis**—The diagnosis of caecal tuberculosis is often made through the accidental discovery of a tumour unaccompanied by any

severe or localizing symptoms (Table XVII p 592) Its recognition has however been greatly facilitated by the method of J Gershon Cohen who has employed the double contrast method of successive injections of barium succeeded by inflation with air

Removal of a piece of tissue for microscopic examination should always be undertaken but though it may have giant cells and present the pathological picture of tuberculosis the demonstration of tubercle bacilli is inconstant

Differential diagnosis from carcinoma or from diverticulitis is by no means easy but as a general rule tuberculosis progresses more slowly and insiduously and affects younger people Examination of the blood may here be of some value the anaemia in patients with tuberculosis of the caecum being less severe than those with carcinomatous involvement of the same region The blood sedimentation rate may be of value

The picture of acute anaemia synchronously with tumefaction in the right iliac fossa is more characteristic of carcinoma of the caecum than of any other condition

Hyperplastic tuberculosis has also to be distinguished from chronic appendicitis and actinomycosis

**Radioscopic diagnosis of both types**—It is not possible always to differentiate the ulcerative type from ulcerative colitis because the general contour of the bowel presents much the same features (Plate XVIII facing p 443) There are evidences of hypermotility general or local coupled with filling defects Nearly all cases of intestinal tuberculosis give the Sierlin sign that is show hyper irritability and hyper motility especially of the caecum with lack of haustral segmentation and irregularity of contour but this sign is not of absolute diagnostic value as any type of ulceration of the colon may produce the same appearances

**Complications**—The main complications of tuberculosis of the bowel are stricture perforation and haemorrhage Actual stenosis and stricture in tuberculous disease progress slowly When a fluctuating tender mass usually on the right side of the abdomen in the appendix area presents itself in a patient known to have tuberculosis it usually portends the rupture of an ulcer Perforation of the intestine by the tuberculous process usually leads to local haemorrhage

**Treatment**—The treatment of intestinal tuberculosis of the ulcerative type is essentially medical The basis should be rest in bed and an easily assimilable diet until the pyrexia has subsided and diarrhoea and dyspeptic symptoms have disappeared It is said that raw milk and fats are poorly tolerated Intraperitoneal injection of oxygen is said to have given good results and deep X ray therapy has been advocated by some workers Of drugs cod liver oil halibut liver oil and similar preparations are indicated Calcium and parathyroid therapy have found favour

Hyperplastic tuberculosis demands surgical intervention and three

surgical procedures have been especially advocated: enterostomy, short circuiting, and total resection of the loop of bowel involved

Tuberculous peritonitis, both of the ascitic and plastic types, may be associated with chronic diarrhoea, especially when tubercular ulceration of the bowel is present in addition

The following illustrative cases may be cited:—

1 Tuberculous ulceration of the large intestine, resembling chronic bacillary dysentery and in radiological appearances, ulcerative colitis

A married woman of twenty-seven was first seen in December, 1933, when she was complaining of prolonged diarrhoea with the passage of dysenteric stools and occasionally blood. These dysenteric symptoms had persisted for 2½ years, after residence in Ceylon, and had led to a diagnosis of amœbic and later of bacillary dysentery. The stools contained pus, blood, and macrophage cells. The white blood count was 7,000 and the lymphocytes numbered 21 per cent. Tuberculous ulceration of the rectum was demonstrated by sigmoidoscopy, and typical acid fast bacilli were obtained from preparations made from the ulcers (Plate XIX, F, facing p 450). In an attempt to perform appendicostomy, April 4, 1934, the lumen of the appendix was found to be obliterated and adherent to the cæcum, and on its removal the cause was ascertained to be tuberculous infiltration of the appendix wall. A barium enema examination, September 21, 1934, demonstrated appearances resembling chronic ulcerative colitis, and a mass of calcified tuberculous retrocæcal glands. Although the patient's general condition greatly improved, the diarrhoea did not entirely cease, and she succumbed to the disease three years later. There was no evidence of any tuberculous focus in the lungs.

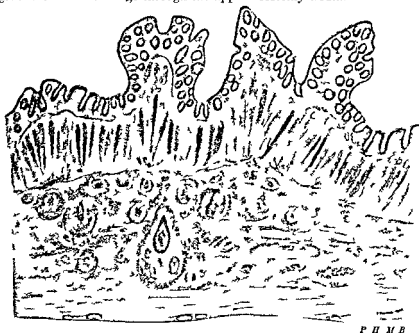
2 A man of fifty six was first seen in October, 1935, complaining of diarrhoea and dysenteric symptoms together with a loss of 23 lb in weight. The stools which were liquid and extremely offensive, contained pus and macrophage cells. By the antiformin method of concentration, acid fast bacilli were demonstrated. Here again, the picture obtained by barium enema was one of chronic colitis, giving the typical smooth appearance and lack of haustration. A bunch of calcareous retrocæcal glands was also visualized. The sigmoidoscopic picture was that of a granular colitis. Although improvement was obtained by a month in hospital, with gain in weight of 14 lb, the prognosis was unfavourable.

3 In November, 1921, the case of a laboratory assistant aged twenty five was investigated. There appeared to be a war infection which commenced in Sylvania in 1917 and had been diagnosed and treated as amœbic dysentery. The patient was ill and emaciated. The numerous stools contained blood, mucus, and macrophage cells. On sigmoidoscopy, it was found impossible to insert the instrument farther than nine inches owing to stenosis of the bowel. Numerous rectal ulcers were visible, and in preparations made from them tubercle bacilli were found. The leucocyte count was 6,000 and the lymphocytes numbered 35 per cent.

Valvular cæcostomy was performed in December, 1921, and was apparently successful, but the patient died a year later from streptococcal septicæmia, the infection originating in the cæcostomy wound. At autopsy, stenosis, sacculation and tuberculous ulceration of the large intestine were demonstrated. The microscopic sections showing the typical histological picture of tuberculosis (Fig 89).

4 A girl of 8½ came from Durban, South Africa, where she had been

suffering from dysentery with blood and mucus in the stools for the past two years. At first she was regarded as an intractable case of amoebic dysentery and was treated accordingly without benefit. On arrival in England in September 1932 the child was very emaciated with œdema of the ankles and an extensive erythematous rash on both legs. There were three or four diarrhoeic stools daily with blood and mucus; the urine contained albumin and granular casts. Before her arrival in London March 1933 an exploratory laparotomy and appendicostomy had been performed on the supposition that the case was one of polyposis and at first the child improved greatly on colonic lavage through the appendicostomy wound.



P. H. M. B.

Fig. 89.—Microscopic section of ascending colon showing tuberculous injection of the longitudinal muscularis layer.

Her appearance suggested tuberculosis. There was a hectic flush on the cheeks, a hectic temperature, fine down on the face and lanugo hairs on the body. Moreover an X-ray of the abdomen showed calcareous retrocaecal glands. The differential blood count was also suggestive, the proportion of lymphocytes being as high as 64 per cent. The diagnosis was completely established when masses of acid-fast bacilli were demonstrated in blood and mucus passed per rectum subsequent to continuous lavage through the appendicostomy wound with 2 per cent sodium bicarbonate solution. Shortly afterwards free fluid was noted in the abdominal cavity. Œdema of the extremities became marked and the patient went gradually downhill.

The remarkable features in this case are the age of the patient and the almost exact simulation from the clinical aspect of acute ulcerative colitis. The barium enema also showed the smooth surface and lack of haustration so characteristic of this disease. The vicarious appearance of tubercle bacilli in the faeces is also to be noted.



## SYPHILIS OF COLON AND RECTUM

It was formerly thought that syphilitic ulceration and syphilitic disease of the large intestine were of great moment, but the attitude of the profession towards syphilis as an intestinal disease has considerably changed during recent years. It is questionable whether syphilis can cause rectal stricture (see p. 511).

Tertiary syphilis was found in the Mayo Clinic series to be the least important factor in rectal strictures as a whole.

There are two types of syphilis of the large intestine—a primary lesion of the ano-rectal region, and a later lesion, or ulceration, occurring in the course of generalized syphilis, the latter being very uncommon. Ano-rectal chancre is fairly common in both sexes, and need not be considered further.

Among the later lesions of intestinal syphilis is the gummatous colitis described by R. Mangot. The gummata may be single or multiple—they may start as small nodules which grow relatively rapidly so that in the course of a few months they measure about 5 cm. in diameter. Later, they ulcerate and a mixed blood-stained exudate escapes, which may give rise to blood and mucus discharges in the stool. Eventually a tubular stenosis of the rectum forms and may lead to obstruction though not to actual fibrous stricture. Of this form of syphilitic colitis the author has encountered only one case in his series.

This was in a ship's steward seen in 1925. A definite history of syphilis of four years' duration was given and the Wassermann reaction was strongly positive. The case was complicated by extensive perianal ulceration and suppuration of glands in both groins, suggesting lymphogranuloma inguinale. The faeces contained blood and mucus. Two definite rectal strictures and a considerable degree of ulceration were revealed by sigmoidoscopy. Prolonged and extensive treatment with neosalvarsan injections and bismuth had no appreciable effect. Eventually colostomy was performed and when the strictures had been sufficiently dilated with bougies the opening was closed a year later. The patient made an excellent recovery and was passing normal motions when examined three years after the last operation.

G. M. Gray has reported two cases from Nigeria which were cured by antisyphilitic treatment (Lockhart Mummery). The best description is given by Charters Symonds (1922) who describes it as involving the lower three or four inches of the gut including the anal margin, and affecting the whole circumference of the bowel. Hard polypoid growths ringing the anal margin, a condition not seen to the same extent in any other form of stricture, are characteristic.

Some cases of syphilitic disease of the bowel are associated with the characteristic condylomata of the anus.

**Diagnosis.**—Diagnosis of syphilitic disease of the bowel is made upon the pathological and sigmoidoscopic appearances and upon positive serological tests for syphilis. The most telling method is,

however, the resolution of the lesions on the institution of antisyphilitic treatment

The radiosopic appearances of extensive syphilitic stricture of the rectum have been described by C J Drucek. There is no ampulla, only a smooth general contracture of the lumen, beginning above the internal sphincter. The stricture is usually long and pencil like, and the opening into it may be funnel shaped.

**Treatment.**—This consists of the usual antisyphilitic treatment, vigorously prosecuted. The actual cautery may perhaps have to be employed for excision and cauterization of the condylomata. When stenosis is present, operative measures, such as short circuiting or colostomy, may be required.

## CHAPTER XXIX

### LYMPHOGRANULOMA AND CHRONIC CICATRIZING ENTERITIS (CROHN'S DISEASE)

#### LYMPHOGRANULOMA INGUINALE (Genito ano rectal syndrome)

**Synonyms** — Climatic Bubo Inguinal Paradenitis Nicolas Favre Disease

**Definition** — Lymphogranuloma inguinale is now known to be due to a filterable virus which entering through a small primary vesicle and travelling via the lymphatics causes inflammation and suppuration of the inguinal glands. At this stage it can cause constitutional disturbances such as pyrexia in severe degree.

In the male buboes are produced in the groin sometimes in the axilla and neck in the female they are rarely seen but there occurs a general lymphoedema of the vagina and labia known as *esthiomène*. In both sexes infiltration of the perirectal tissues takes place resulting in ulceration and stricture known as the genito ano rectal syndrome. It is with the rectal aspects of lymphogranuloma that this account is mainly concerned.

Knowledge on this subject is comparatively recent.

**Ætiology** — The bubo termed climatic bubo is well known in tropical practice it is especially prevalent among Europeans in West Africa India China Malaya Japan the southern Mediterranean the West Indies and South America. In France P. M. Durand J. Nicolas and M. Favre (1913) described this condition as Lymphogranuloma inguinale and it has been realized that the virus is widespread in France and Germany and indeed throughout the whole of Europe. Since 1933 several cases have been reported in England. The writer had one case (1935) in a woman from Soho London whose husband was similarly affected. In the United States this disease has been recognized in all its manifestations especially among the negro population.

**The virus** — In 1930 S. Hellerström and L. Wassen transmitted the virus obtained from the pus of inguinal buboes to monkeys, intra cerebral inoculation produced a meningo encephalitis. An emulsion prepared from the cerebral tissues produced on intra lermal injection a local manifestation known as the Frei-Hoffmann reaction. The virus of lymphogranuloma belongs to the filterable group and it has been shown by G. M. Findlay (1932) that intraglandular injection of guinea

pigs produces an inguinal bubo in every case, this method can therefore be employed for diagnosis. The most reliable test at present in use (Findlay) is, however, the intracerebral inoculation of white mice, which produces an encephalitis. The serum of an infected person contains antibodies, hence a protection test has been devised by mixing equal parts of the serum from a bubo patient with an emulsion of mouse brain diluted 1:5 in normal saline, and kept for twelve hours in an ice-box at 4° C. When injected in doses of 0.5 c.c. intracerebrally, no reaction is produced.

Recently Y. Miyagawa (1936) has found in Japan that a squirrel (*Entomias asiaticus orientalis*) is highly susceptible to intratesticular and intracerebral inoculation. He has moreover, been able to cultivate the virus in chorio-allantoic membrane of the chick embryo in tissue culture.

Ravaut, Levaditi, Lambing and Cachera, finding that they were unable to inoculate monkeys intracerebrally with contaminated material from the rectum, devised a method of inoculating a portion of tissue removed from a case of ulcerative proctitis under the skin of a guinea pig. After a few days the inguinal lymphatic gland was excised, emulsified and used as an intracerebral inoculum for a monkey, typical meningo-encephalitis being reproduced.

**Symptoms.** *Primary sore*—M. Durand (1918) and independently, H. M. Hanschell (1926) described, as the primary lesion of lympho-granuloma, a small herpetiform vesicle or ulcer on the prepuce, which heals up in a few days. From this point the virus travels via the lymphatics to the inguinal glands. The incubation period before the appearance of adenitis appears to be from three weeks to two months. The disease generally commences with a remittent pyrexia which may precede the localizing signs. Soon afterwards subacute inflammatory swellings of the inguinal glands, unilateral or bilateral, are noted. Usually, in well marked cases the internal iliac glands are also implicated.

The affected glands gradually enlarge and after a period of several weeks—or even months—the swellings break down and suppurate. Sometimes they subside without suppuration and are hard and extremely tender. Fistulous tracks may form, from which a serous and sticky fluid exudes. If much lymphatic tissue is removed by operation, an elephantoid condition of the scrotum and leg may ensue.

Chimatic buboes in the groin have definite physical characteristics which serve to distinguish them from other suppurative lesions, such as septic buboes, plague and filariasis. Sometimes painful effusions, probably due to toxic absorption, are noted in the larger joints. Extragenital infections have been recorded—on the tongue, followed by glandular enlargements in the neck (W. Curth), in the axilla (S. Hellerstrom), and on the foot (Lepinez and Grevin). The author has also seen the cervical glands affected in an Indian seaman with inguinal buboes.

Patients with rectal lymphadenoma usually present the symptoms of stricture, and pass malformed or ribbon shaped feces. Tenesmus, intestinal colic, and alternating diarrhoea and constipation are common. Usually there are associated rectal fistulae.

**Rectal lesions**—Nearly all authorities are now agreed that non-malignant strictures of the rectum, in both sexes are generally not syphilitic in origin but are due to the virus of lymphogranuloma. In 1932 Frei and Koppel applied the intradermal test in cases of rectal stricture where syphilis could be excluded and obtained a positive result. O. Jerveld (1930) originally suggested the term *genito ano* rectal syndrome for the symptom complex seen in women who present the combination of *esthomené* (vulval elephantiasis) with rectal stricture. In 1930 the same investigator reported upon twenty three cases in all of which the intradermal test was positive. Since then, results have been confirmed by French workers. W. Frei (1932) reported that 80 per cent of cases presenting the *genito ano* rectal syndrome have given positive intradermal tests. Bensaude and Lambling in Paris (1931) found 86.6 per cent of strictures and 92.5 per cent of proctitis cases to be *Frei* positive. They recorded twenty one cases of anal stricture in women in twelve of the fourteen cases manifesting no other lesion. Frei's intradermal test was positive. In the United States, H. P. de Wolf and J. V. Van Cleave found, among 1,010 cases subjected to the intradermal test, fifty eight positive reactions, of which fifty five were cases of lymphogranuloma and three had *ano* rectal disease.

The sexual incidence of rectal strictures has been remarked upon by nearly every observer, it is very much more frequent in the female than the male the proportions being about six to one. In India, however the proportions appear to be reversed. Rajam, in a review of 183 cases in Madras, reports rectal strictures in 18 male and 8 female patients.

It is now generally recognized from the work of Bensaude and Lambling and of Ravaut, Levaditi, Lambling and Cachera, that the frequency of rectal stricture in Berlin and Paris is due to homosexuality, and the primary lesion is probably in the vicinity of the anus.

The position of the stricture has been noted by many surgeons. Perret in fifty six cases, gives its situation as follows. At the anus, in four, less than 6 cm. above the anus, in thirty two, between 6 and 9 cm. of anus, in fourteen, in the colon, in six. R. Barthels and H. Biberstein believe that in the majority of cases the stricture lies from 2 cm. to 6 cm. above the anus. The association of vulval and *ano* rectal lesions has been recognized by many workers.

The ulcers of the bowel vary in appearance according to their duration. They can be distinguished from other rectal ulcers, on sigmoidoscopic examination, by the amount of fibrous tissue present, and also by the general history of the case.

The course of the disease from the initial lesion of lymphogranuloma

virus to the production of the genito ano rectal syndrome appears to be as follows —

In the female, if the initial sore occurs in the upper two thirds of the vulva, the virus will, in a great proportion of cases, pass to the inguinal glands and, as in the male, an inguinal bubo will result. If, on the other hand, the lesion is situated towards the posterior part of the vulva or in the vagina, then the infection will pass to the intra-pelvic glands and lymph plexuses which drain the lower part of the rectum, and a retrograde lymphangitis takes place. In the walls of the rectum the maximal incidence occurs between 2 and 6 cm. above the anus—that is, at the lower border of the ampulla just below its upper margin—at the situation where strictures are most common.

T. R. Peyton in his classification of rectal strictures due to this virus, finds that it at first produces proctitis; then, especially in women, is associated with esthiomène and anal stricture; later, annular and tubular rectal strictures, and finally, rectal communicating strictures from ulceration between rectum, bladder, vagina, prostate and seminal vesicles.

Rectal stricture due to the virus of lymphogranuloma must be rare, at least in England. From an analysis from 3,068 sigmoidoscopic examinations made during fifteen years, in the Hospital for Tropical Diseases, there were only two cases of rectal stricture giving a Frei-Hoffmann reaction. The particulars of these two cases are given below.

The first was seen in 1934 in a man aged sixty who had a hard rectal stricture 3 cm. from the anus, below the stricture the surface was ulcerated and there were numerous fistulae. The intradermal Frei-Hoffmann reaction performed with Findlay's antigen was positive. It appears that twenty-two years previously, in China, the patient had contracted lymphogranuloma inguinale, with suppurating buboes on both groins, of which the scars still remained. Three years afterwards, rectal ulceration with fistula formation commenced and he passed blood and mucus with the faeces. For seventeen years he had suffered severely from the effects of this rectal stricture. Both Wassermann and Kahn reactions were negative. Incision of the stricture with dilatation resulted in great improvement.

The second case, in a male patient from South America, came under the care of N. H. Farley in July, 1935. The patient gave a history of rectal trouble following climatic bubo and extending over a period of nine years, with fistula formation and a muco-purulent discharge from the rectum. Although he had acquired syphilis many years previously, the Wassermann reaction both in the blood and cerebro-spinal fluid was negative. There was also a history of several attacks of gonorrhoea including a gonorrhoeal proctitis. In 1926 he had climatic bubo involving the glands of both groins, and at this time there was a sore inside the rectum near the sphincter. The Frei-Hoffmann intradermal reaction was positive with mouse strain antigen as well as with pus from buboes.

Examination showed a constricted, firm and fibrosed anal canal and fibrotic proctitis. A hard craggy projection was found in the floor of the rectum 9 cm. from the anus. Histological examination of a small portion revealed

no carcinomatous changes. During instrumentation a copious discharge of fluid pus took place from a perianal sinus.

The importance of the following case to British practitioners is self-evident.

A fatal and extremely advanced and undiagnosed case was seen in July 1941 in a woman of forty-five. Undoubtedly the original infection had been contracted in England in 1920. Two years after marriage she began to suffer from rectal ulceration which was thought to be piles. Since that time for a period of eighteen years constipation had been acute and pararectal fistulae had appeared. Gradually signs of subacute obstruction became more



Fig 90—Lymphogranuloma inguinale—stricture of the rectum with fistulae and ano-genital elephantiasis

(After R. Bensoude and A. Lambing)

and more apparent necessitating an exploratory laparotomy during which the true diagnosis does not appear to have been appreciated. The stools from this stage onwards resembled those of ulcerative colitis and severe anaemia rapidly developed. A typical ragged rectal stricture was demonstrated by digital examination. There were numerous radiating discharging fistulae in both buttocks and the Frei-Hoffmann reaction was positive. She died shortly afterwards from intestinal obstruction.

*Ocular complications* have been described by J. A. Macnie (1941). These consist of uveitis and keratoconjunctivitis. Sometimes the whole globe is covered with granulomata and monkeys have been infected with extracts of this material. The Frei-Hoffmann reaction is positive.

W. Curth and his associates (1940) have also isolated the lymphogranuloma virus from three cases of chronic granulomatous conjunctivitis with secondary pannus by tissue culture and animal inoculation (mouse and monkey). The former method was found more practicable. Treatment with sulphanilamide was effective in stopping the active process.

**Diagnosis**—The symptoms produced by this syndrome are mostly those of rectal stricture with intermittent attacks of diarrhoea. The clinical diagnosis is made in the first place by digital examination of the rectum. A hard fibrous and annular rectal stricture certainly suggests this condition. Sometimes the indurated mucous membrane imparts a nodular warty sensation to the examining finger (Fig. 90).

The diagnosis is confirmed by the intracutaneous reaction (intradermal test) which is now known as the Frei-Hoffmann reaction. The antigen is prepared from the diseased gland tissue or from pus from the buboes. Pus is withdrawn from a gland which has undergone softening but not fistulation and is mixed with physiological saline in a sterile tube in the proportion of one part to five. Thus prepared it is heated to 60° C. for two hours over a water bath and the following day to 60° C. for one hour. The antigen is preserved at a low temperature unexposed to light. Tests must be repeated every three months and should give *negative* reactions in the skin of normal and control patients.

Other sources of antigen consist of emulsified glands and more recently of similarly prepared mouse brains infected with this virus. Some doubt exists on the score of pseudo reactions caused by normal brain tissue. Better results have been obtained by S. E. Sulkin (1941) and collaborators by employing *Lygranur* prepared directly from virus on egg yolk sac embryo. W. Frei (1939) has drawn up minute instructions for the preservation of the antigen: it must be protected from light and kept on ice at the lowest possible temperature—the colder it is the longer the vaccine retains its efficacy. The test itself is carried out on the same lines as the Dick sensitization test: 0.1 c.c. of the antigen being administered intracutaneously in the forearm where it causes a wheal 9 to 10 mm. in diameter. A positive result usually appears between twenty-four and forty-eight hours after



the injection in the form of a circle of infiltration  $1\frac{1}{2}$  to 3 inches in diameter (Fig 91) German writers have noted an infiltrated hard mass which may persist for a few days. The Wassermann and Kahn reactions are negative in the uncomplicated disease.

A. L. Taussig and M. Somogyi (1940) assert that hyperglobinæmia is constantly present in the serum of lymphogranuloma and that this test is of service in differentiation from *granuloma venereum*. C. M. McKee, G. Rake and M. F. Shaffer have devised a complement

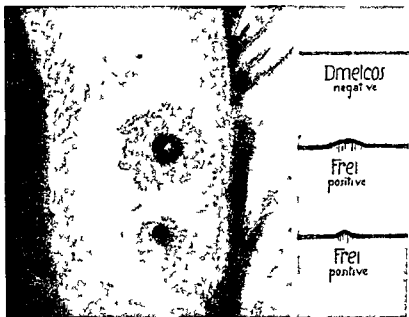


Fig 91 —Lymphogranuloma inguinale illustrating Dmelcos negative reaction and two positive Frei Hoffmann intradermal reactions

(After R. Bessaud and A. Lambert)

fixation test using *Typhimur* (M L) as antigen. In this case the preparation was made from the triturated lungs of infected mice. H. M. Robinson (1940) emphasizes the necessity of controlling this test with the parallel inoculation for chancre (Dmelcos vaccine) which is now known as the Ito Reenstierna test.

**Treatment**—Treatment of rectal stricture due to this virus is a difficult matter. Palliative measures consist in dilating the stricture by graduated bougies and injecting antiseptic solutions to cure the ulceration.

Operative treatment depends upon the type of stricture present. Lockhart Mummery gives the following alternatives: internal

proctotomy complete proctotomy excision of the stricture or of the rectum, and colostomy

*Dathermic dilatation*—According to Bensouda and Lumbing dathermic dilatation appears to be the best form of treatment for the stricture. It is superior to simple dilatation with the nutal bougie or rubber catheter. A treatment of about twenty minutes every two or three days, for ten or twelve applications is recommended.

*Treatment of the bubonic stage* (chilicatic bubo)—In the lymphogranulomatous stage, the inguinal glands when they are inflamed but discrete can be excised the spread of further mischief being thus prevented. This has been performed by A. H. McIndoe with conspicuous success. But the surgical laying open of suppurating glands or sinuses is contra-indicated because usually the gland tissue becomes secondarily infected and a permanent lymphatic sinus may ensue. During the acute stage treatment should consist of rest and the application of soothing dressings.

*Protein shock therapy* (non specific protein shock) by intravenous injections of killed typhoid paratyphoid vaccines commencing with 50 million and increasing gradually to 200 or even 300 million is often followed by the subsidence of inflammation. Generally two or three reactions are required before the buboes dry up.

*Medicinal treatment*—In the chronic stages applications of mercury ointment promote healing. Intravenous injections of tartar emetic (sodium antimony tartrate) have been much employed, eight to fifteen injections of 5-10 c.c. of a 1 per cent solution are required. The pentavalent compounds of antimony (stibosan and neostibosan) in recognized doses have also been employed with apparent success.

In recent years sulphonamides especially sulphapyridine have been found specific for the virus of lymphogranuloma. Full doses of 4.6 gm. are necessary in courses of five days duration. They have been employed also as an adjunct to surgical measures in the rectal form and are useful in healing up rectal ulceration.

F. O. MacCallum and G. M. Findlay have shown that in experimentally infected mice sulphonamides are of definite value.

In man R. Montel (1938) in Indo China has found the French preparation rubiazol curative if given in courses over a prolonged period. K. V. Earle in Trinidad has reported that sulphapyridine (M and B 693) is beneficial in doses of 1.5 gm. daily. C. B. Kennedy, J. K. Howles, G. Smullen and M. E. Kopfler report favourable results with neoprontosil average total dosage 98 gm. and duration of treatment 34 days. R. O. Stein (1940) in 35 cases (32 acute and 3 chronic) found that rapidity of disappearance of lesions corresponded with concentration of sulphapyridine in the blood. Raising the level from 4-6 mgm. per cent to an average of 10.16 mgm. reduced the average time for subsidence of the bubo from 2.6 to 1.3 weeks but it was found advisable to continue treatment for one week beyond the period of subsidence. In the majority of cases the Frei-Hoffmann reaction became negative.

## CHRONIC CICATRIZING ENTERITIS

**Synonyms**—Regional Ileitis, Crohn's Disease

This rare disease is included in this work in order to draw more general attention to the condition and to emphasize the possible necessity of differentiating it from other forms of diarrhoea and dysentery.

Regional ileitis manifests itself mainly in the terminal portions of the ileum, but it is possible that inflammatory ulcerative and granulomatous patches in the jejunum, ileo caecal region, and circumscribed areas of the colon are of the same nature.

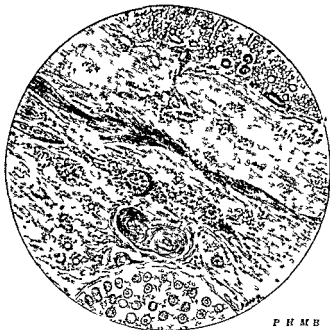
**History**—The importance of benign, non specific granulomata affecting the small intestine was first brought out by Crohn, Ginzburg, and Oppenheimer in 1932. On this localized granuloma the name of regional ileitis was bestowed, although in America it has since become more generally known as Crohn's disease. Later, in 1934, Crohn enlarged his concept of regional ileitis to include widespread involvement of the small intestine.

Almost all the recorded cases of this condition are to be found in American literature, only a few instances have been found in Great Britain. In 1933 Molesworth reported a single case with stenosis of the ileo caecal valve, and in 1934 Jackman described two cases as localized hypertrophic enteritis. In 1935 Dickson Wright exhibited two more at the Medical Society of London. In 1936 Barbour and Stokes gave an excellent synopsis of regional ileitis, together with a completely worked out account of an autopsy on a mental patient. This patient had also been investigated by the author at one stage of his illness. P. W. Brown, J. A. Bagen, and H. M. Weber (1934) have given a very complete account of Crohn's disease, based upon eighteen patients in whom the diagnosis was established in seventeen instances at operation, and in one by radiographic examination. The disease is apparently more common in males; in Crohn's original series, there were more than twice as many males as females. The age period is noteworthy. Crohn originally described the condition as chiefly affecting young adolescents, but cases have since been reported involving all ages. The age of the case reported by R. F. Barbour and A. B. Stokes was sixty three.

**Etiology.**—The ileum, the jejunum, and small portions of the caecum may be involved. It is now recognized that the large intestine is also quite commonly affected. T. G. James describes a case in which the large bowel, from the distal part of the transverse to the pelvic colon, was implicated. The descriptions of regional ileitis by surgeons who have performed exploratory operations are all strikingly similar. There is an inflammatory process, sharply localized in area, involving all layers of the intestinal wall and associated with hypertrophy, the whole mass simulating in rigidity and appearance a stiff rubber tube. Naturally, this fibrotic thickening has been suspected of

being tuberculous in origin, but no subserous tubercles have ever been observed

That the disease is progressive is shown by the fact that in some patients who have undergone resection of the ileo caecal portion of the intestinal tract, the disease has spread into the proximal portion of the ileum. No light has so far been shed upon the nature of the virus which may give rise to this chronic inflammation. Lakely and Lisa (1939) have suggested that it may be allied to that of lymphogranuloma



P H M B

Fig 92 —Microscopic section of lower ileum in chronic cicatrizing enteritis (Crohn's disease) showing fibrosis mainly of the submucosa and giant cells with included crystalline bodies. The circular muscular coat is also affected. (Author's case.)

inguinale. They found at autopsy multiple granulomata of the ileum in a negro with the genito-ano-rectal syndrome.

**Pathology**—The pathological condition consists of a fibroblastic reaction with an infiltration of polymorphonuclear leucocytes and round or plasma cells. The mucous membrane of the parts affected is ulcerated and the submucosa much thickened by cellular infiltration. A striking feature is the presence of giant cells of the foreign body type in the plane between the longitudinal and circular muscular coats in close relationship to the ganglion cells of Auerbach's plexus; these cells contain hard crystalline bodies of variable shape and size (Fig 92). Everywhere the reaction is attended by great thickening of the bowel walls, with encroachment on the lumen.

Every effort which has been made by different investigators to demonstrate tubercle bacilli (mainly by the injection of material into guinea pigs) has signally failed. G. Hadfield (1933) has given the best description which has yet appeared of the histology. The earliest and possibly specific histological lesion is lymphadenoid hyperplasia with the formation of giant cell systems which are also present in the regional mesenteric glands. Viewed as a whole, the histological picture cannot be distinguished from that of tuberculosis. Ulceration and fistulae are secondary to the primary lesion.

**Symptoms**—An almost constant complaint is pain which when the disease is confined to the jejunum, is apparently localized to the umbilicus when the caecum and ascending colon are involved together with the ileum the pain is in the upper portion of the abdomen. Diarrhoea is almost invariable and the information so far obtained suggests that its presence or absence is in some way connected with the situation of the lesions and the extent of the pathological changes. Usually the stools are loose and watery without much urgency and without visible blood. Vomiting is an important symptom. Most of the patients have bouts of pyrexia and generally there is loss of weight. Intestinal fistulae occurred twice in eighteen cases in Brown, Bergen and Weber's series. There is usually a mild secondary anaemia and a mild leucocytosis of 10 000.

Crohn divided his cases into four clinical types a classification which has since been accepted—

- 1 Acute intra abdominal disease with peritoneal irritation
- 2 Ulcerative enteritis
- 3 Chronic obstruction of the small intestine
- 4 Persistent intractable fistulae in the right lower quadrant

In the first type appendicitis may be simulated in the second the patient complains of colic and diarrhoea and there is commonly a constant low grade pyrexia. The type of case with peri umbilical pain and with blood and mucus stools three to five a day as in the series recently described by L. Barrington Ward and R. E. Norrish closely simulates ulcerative colitis. In the third type incomplete obstruction is encountered with violent cramps, borborygmi and occasional attacks of vomiting and constipation. A palpable mass may be present and the obstruction may be complete. In the fourth type intractable fistulae follow the operative drainage of a supposed appendicular abscess.

**Diagnosis**—The cicatrization does not, as a rule give rise to any gross obstruction so that in the absence of a palpable mass the clinical picture is quite indefinite without radiography diagnosis may be impossible. Sometimes even it is only after resection that tubercle and carcinoma can be excluded.

The X-ray appearances of the inflammatory processes in the small intestine and in the large are practically the same. There is mural thickening with consequent stenosis and stiffening and shortening of

the involved portion with destruction of the mucosa. A radiographic examination demands close scrutiny of each individual segment by observing the descending opaque meal. Careful investigation of the terminal portion of the ileum after it has been distended as the opaque enema passes through the ileo cæcal orifice is also necessary. Kantor says that in the extreme narrowing of the terminal ileum the string sign is produced. A. W. Galambos and W. Mittelman, J. L. Kantor, H. M. Weber, and others all believe the X ray appearances to be typical and diagnostic when the terminal ileum is involved. Sigmoidoscopy is usually of little avail in arriving at a diagnosis.

The differential diagnosis has to be made from malignant disease, diverticulitis, hyperplastic tuberculosis, lymphadenoma, actinomycosis, and syphilis, the localized inflammatory masses must be distinguished from chronic appendicitis, Meckel's diverticulum, chronic intussusception, and twisted ovarian cyst. Cases with diarrhoea have to be differentiated from the various types of colitis, especially ulcerative colitis, and dysentery.

**Treatment**—The treatment of Crohn's disease is generally admitted to be a surgical problem. The main possibilities are to short circuit the lesion to resect it, or to short circuit it first and resect later. C. G. Mixer prefers resection but admits that the mortality is high. The disease cannot be treated with any degree of success by medical means.

B. B. Crohn (1939) emphasizes once more the necessity of early recognition of the condition even before the appearance of characteristic radiological changes. S. F. Marshall (1940) has made follow up observations on 48 cases of regional ileitis over a period of seven years. Of these, 29 were operated on with 2 deaths. Resection of individual loops of intestine was performed in 22 patients without a fatality. The two stage method of resection is the operation of choice. Recurrences are probably associated with incomplete removal of the affected bowel and for this reason wide excision of the affected loop is indicated.

A. M. Snell (private communication) has made the interesting and pregnant observation that the sprue syndrome may supervene after removal of recurring cicatrizations of the jejunum and upper ileum.

## CHAPTER XXX

### DIVERTICULITIS, INTUSSUSCEPTION, HÆMORRHOIDS, FOREIGN BODIES IN THE RECTUM

#### DIVERTICULITIS AND DIVERTICULOSIS

It is beyond the scope of the present work to describe in detail the large amount of research which has been devoted to this subject in recent years. The conditions will be dealt with only in so far as they enter into the differential diagnosis of dysenteriform diseases.

*Diverticulosis* may be described as sacculculon occurring throughout the lumen of the large intestine. This condition is usually unproductive of symptoms save in a comparatively small number of cases in which inflammatory changes are taking place. *Fæcoliths* which form in the diverticula may not be discharged into the lumen of the colon but remain imprisoned thereby causing inflammation or *diverticulitis*.

Acquired diverticula may be single or multiple. Cruveilhier is reported to have found 200 in a single colon. The individual diverticula differ in size even in the same segment of the bowel and may vary from almost microscopical size to pouches 4 cm. in diameter although the average is about 1 cm. E. I. Spriggs and O. A. Marzæ (1927) reporting on a radiological study of 1 000 cases found that diverticula of the colon were present in 10 per cent. From autopsy records of 1,925 cases (1924-28) Rankin and Brown at the Mayo Clinic found diverticula in 5.2 per cent. It is probably a fair estimate that the incidence of diverticulosis in those over forty is about 5 per cent. and in only some 17 per cent. of these are symptoms of diverticulitis present.

H. C. Edwards found that the youngest in his series of cases was thirty-two. On the average symptoms appear to arise first at about fifty years of age. The influence of sex is only very slight, in the series recorded by Rankin and Brown 60 per cent. occurred in males.

Diverticula are formed most commonly in the sigmoid colon but they may be distributed throughout the large intestine, usually with increasing frequency from the right to the left side of the bowel.

**Ætiology**—It is by no means clear whether the majority of diverticula are congenital or acquired but the consensus of medical opinion is that diverticula of the large intestine are traction diverticula. It was originally suggested by Kiebs that they were especially likely to occur at the mesenteric attachment through weakness at that particular point, but recent observers are by no means in agreement that this is

the true explanation H C Edwards points out that the circumference of the intestine through which diverticula emerge is governed by two anatomical factors—the disposition of the longitudinal muscle fibres and the mode of entry of the blood-vessels. The sites of election for the formation of diverticula are arranged in two rows immediately to the mesenteric side of the two lateral muscular tæniæ. Each diverticulum starts by the migration of a wedge-shaped process of mucous membrane through the circular muscle fibres at the point of entry of a blood vessel. Once the process has taken place, pressure exerted from within the bowel forces the wedge of mucous membrane further along the connective tissue sheath of the blood vessels, and eventually a flask shaped diverticulum is formed. When this stage is reached, the circular muscle fibres between the diverticula steadily contract, so that the pouches become progressively larger, and at the same time the lumen of the bowel becomes narrowed. From these considerations it seems impossible to escape the view that diverticula are due to forces arising within the bowel wall itself.

**Pathology.**—The processes which occur in the diverticula eventually produce inflammatory changes, so that perforation, stricture and fistulæ result. In the great majority of cases, however, diverticulitis runs a chronic, uncomplicated course. It is generally acknowledged that pathological changes occur most frequently in the pelvic colon and rectum, probably because of the fæcal stasis which arises at these situations. It is pointed out that, at this level, the nature of the fæces, which are firmer and more compact, tends to prevent the diverticula from becoming emptied of their contents. On the other hand, the right side of the colon, which normally contains liquid fæces, is far less likely to be subject to impaction.

The local inflammatory changes commencing in the mucous membrane subsequently spread to the submucous coats and cause ulceration, later they spread to the other coats of the bowel and to the mesentery, producing perisigmoiditis. The chronic thickening of the mesentery results from spread of the inflammatory process, and some times may be due to perforation into the mesentery. Perforation of a diverticulum may produce a local abscess or fistula, rarely, however, does it bring about general peritonitis. It is not uncommon for a vesico-intestinal fistula to result after the formation of an intrapelvic abscess, or after the adhesion of the thickened sigmoid to the bladder.

**Symptomatology.**—The most common symptom is some form of abdominal pain, which may consist of ill defined subacute sensations of discomfort similar to those felt in chronic amœbiasis. Usually the pain is situated in the left lower quadrant or lower abdomen, and it may be accompanied by localized tenderness, muscular rigidity, nausea, vomiting and pyrexia. The exact situation of localized pain, when present, is probably dependent upon attachment to, or perforation of some other viscus. Diverticulitis with the accompanying pain, pyrexia and leucocytosis, closely resembles appendicitis, but is on the left side,



TABLE XVII.—PHYSICAL CHARACTERISTICS OF TUMOURS OF THE COLON

	CARCINOMA	DIVERTICULITIS	RICHARDSIASIS	AMOEBIASIS	TUBERCULOMA	ACTINOMYCOSIS
Size and Shape	Fusiform or round	Indefinite and diffuse	Irregular lobulated tumours	Nodular	Oval or round	Indefinite masses
Position (in order of frequency)	Sigmoid caecum transverse colon	Sigmoid caecum	Sigmoid transverse colon	Sigmoid	Caecum	Caecum mainly
Mobility	Mobile in early stages Later fixed to surrounding structures	Fixed	Not usually mobile	Mobile	Fixed	Fixed
Hardness	Hard and firm	Plastic	Extremely hard	Comparatively soft	Hard	Diffuse
Tenderness	Usually not tender	Not tender unless in acute stage	Not tender	Definitely tender	Not tender	Tender
Constancy	Preserve their size and shape from day to day	Inconstant vary in shape and size from day to day	Remarkably constant in shape and position	Constant in shape and position	Constant in shape and position	Inconstant, usually accompanied by sinusses



*Photo : Dr Bertram Shiras*

Barium enema, showing stenosis and ulceration of the lower sigmoid and rectum in a case of diverticulitis producing dysenteric symptoms. The cæcum had been removed eleven years previously for this condition.



*Photo : Dr. G. Mather Cordner.*

Barium enema of extreme case of diverticulosis of the



Ph D F G 001

RADIOGRAPH OF A TUMBLER IN THE  
RECTUM (*see p 58*)  
(*Mr H E Croft's case*)

PLATE XXI

and it may be acute, subacute, or chronic. Constipation is usually a constant accompaniment, especially when tumefaction has taken place, and an actual lump can be felt. On the other hand, diarrhoea alone may be present, being usually of a dysenteriform character and accompanied by tenesmus with passage of blood, pus, and mucus.

In the author's series are three cases in which a diagnosis of dysentery had been made on the nature of the stools, which in one instance consisted for a time almost entirely of blood stained mucus. The explanation of these cases seems to be that the diverticular mass is situated in the lower sigmoid and is the seat of a considerable degree of ulceration and suppuration. In some cases a continuous discharge of muco pus takes place, suggesting the presence of an abscess which has ruptured into the lumen of the bowel. When ulceration of the bowel has taken place in conjunction with diverticulitis, then the resemblance to the dysenteric syndrome may be very close.

The most striking case in the author's series was the following —

In 1933 a professional man, aged sixty four, had been passing blood in his motions for twenty years, for two years they had periodically consisted of blood stained mucus. On his return from a voyage to India the diarrhoea became so marked (six to twelve stools a day) that he was thought to be suffering from amœbic dysentery. In 1924 a sausage shaped mass which was believed to be a carcinoma was removed from the right iliac fossa and was found to be diverticulitis. Repeated microscopic examination of the faeces revealed no amœbæ nor could any dysenteric lesions be seen by sigmoidoscopy. The barium enema (Plate XX) showed a constriction of the sigmoid at 25 cm. and a definite area of diverticulitis immediately above it. In April, 1934, he had a sudden illness, with rigors and pain over the liver which had to be opened, when the cause was found to be a liver abscess (streptococcal). He made a good recovery, but eventually a left sided colostomy had to be performed on account of intrapelvic suppuration.

It was definitely proved that the whole illness was due to complications of diverticulitis, no evidence of neoplasm was forthcoming.

Tumefaction in the course of the sigmoid colon is a common finding and indicates inflammatory changes in the neighbourhood of segmental diverticulitis (Table XVII). According to Rankin and Brown, blood *per rectum* is also quite common in diverticulitis, and this has to be taken into account in making a differential diagnosis from carcinoma. Symptoms referable to the bladder often occur and usually betoken serious complications, diverticulitis being the most frequent cause of vesico colic fistula.

**Complications.**—Perforation of the large intestine is comparatively frequent, and J. A. Bagen and F. W. Cox found that it occurs more often in diverticulitis than in carcinoma. The formation of a localized intraperitoneal abscess is perhaps the most common complication. There appears to be no conclusive evidence that diverticulitis is apt to give rise to carcinoma.

Amœbic infection may be grafted upon diverticulitis, and may then be responsible for some of the symptoms. This complication has been

noted twice in the author's series. There is no evidence however that a previous dysenteric infection in any way predisposes to diverticulosis. This point has been investigated in seventeen consecutive cases under the author's care.

**Diagnosis**—The diagnosis of diverticulosis and diverticulitis is made chiefly by X ray examination. In the early stages the X ray appearances are those of extreme irritability of the colon. The signs are those of spasm and excessive motility, all degrees being visible. At first there is marked and irregular haustration. The actual diverticula are visualized as pinhead elevations and are usually seen in the sigmoid colon. Then there is the saw edge appearance and finally well marked diverticula with wide mouths can be visualized after partial evacuation of the barium enema. (Plate XX.) Diverticula containing fecoliths give the appearance of grape like projections from a broad stem represented by the contracted and spastic bowel.

Proctoscopic and sigmoidoscopic examinations are usually of little value except when the lesion is extremely low. Sacculation of the mucosa is generally present.

**Treatment**—The treatment of diverticulitis is mainly medical only when complications are present should surgical interference be contemplated. In acute cases treatment should consist of rest in bed, a residue free dietary, the application of ice to the lower abdomen and rectal irrigation with normal saline or 2 per cent sodium bicarbonate. When the acute condition has subsided a bland diet should be instituted and some mineral oil preparation such as unjol or petrolagar should be given in small doses (1-2 drachms three times daily). This is preferable to giving a large dose once a day as is commonly practised.

In a patient who presents symptoms of diverticulitis such a régime must be continued indefinitely.

## INTUSSUSCEPTION

Intussusception is a surgical disorder but it is nevertheless one of outstanding importance to the student of dysentery on account of its tendency to occur in patients affected with one or other of the dysenteric disorders especially bacillary dysentery. So frequently may this complication occur that it is a comparatively common surgical error to operate upon very acute cases of enteritis or bacillary dysentery in small children on the presumption that they are suffering from intussusception. On the other hand intussusception may closely simulate bacillary dysentery.

Acute intussusception occurs when one portion of the bowel becomes invaginated into an immediately adjacent portion almost invariably it is the proximal which is invaginated into the distal. An intussusception consists of three parts: 1 the entering or internal tube, 2 the returning or middle tube and 3 the sheath or outer tube the intussusciens. The inner and middle tubes together form the intussus.

*capitum* the neck is the junction of the entering layer with the mass and the part which advances is known as the *apex*. The mass which constitutes the main intussusception gathers solidity as it advances. Naturally, with increasing pressure the blood supply of the inner layers of the intussusception tends to be cut off. Gangrene may therefore ensue.

The following varieties of intussusception are recognized —

Ileo ileal	about 8 per cent
Ileo-colic (ileo ileal which has passed through the ileo cæcal valve)	36
Ileo cæcal (with the ileo cæcal valve at the apex)	46
Cæcal (invagination of the caput cæci)	2
Colo colic (colon invaginated into colon)	8

In a few cases intussusception in children arises from irritation caused by a polyp, a submucous lipoma, or a Meckel's diverticulum. In bacillary dysentery in children under ten years of age other infections of the intestinal tract, especially with *Ascaris lumbricoides*, may be a predisposing cause.

**Symptoms**—Intussusception accounts for the majority of cases of acute intestinal obstruction in children in the first two years of life. It usually occurs in a well nourished healthy child. He is suddenly seized with severe abdominal pain causing screaming and contraction of the legs. Periods of exacerbation are followed by great exhaustion and sweating. Screaming fits are followed by pallor. Vomiting is the usual accompaniment and the vomit at first consists of gastric later of intestinal contents. Constipation may be complete but usually diarrhoea sets in with blood and mucus in the stools. Indeed the discharge of blood and mucus from the anus is so important that without its aid diagnosis is rarely achieved. Herein lies the great difficulty of making a diagnosis in children suffering from dysentery before the intussusception actually takes place. W. S. Perrin and E. C. Lindsay noted blood and mucus in 89 per cent of the 400 cases they pass in review. The bleeding arises from venous congestion and in addition there is considerable sloughing of tissues.

An elongated sausage shaped tumour can usually be palpated. Its situation naturally varies considerably, usually it begins in the right iliac fossa and advances along the course of the colon. Sometimes the intussuscepted bowel may even protrude from the anus.

**Diagnosis**.—One of the chief difficulties in diagnosis is the differentiation from other forms of acute intestinal infection and of obstruction. In infants the question of its differentiation from acute appendicitis may arise. But the sudden onset, the extreme pain with accompanying prostration and the presence of a tumour which may protrude from the anus should determine the diagnosis. The passage of blood and mucus in the absence of faeces is characteristic but microscopic examination of the exudate is of little avail as it closely resembles that of acute

bacillary dysentery (see p 81) Only in chronic intussusception which usually occurs in adults, is radioscopy by means of a barium enema of any direct diagnostic value The need for differential diagnosis from Henoch's purpura may occasionally arise

When other data are typical, the diagnosis should be made even in the absence of an abdominal mass, as delay in operation is fatal

**Treatment**—The treatment of intussusception is surgical

### HÆMORRHOIDS

Hæmorrhoids are usually sufficiently distinctive to be recognized at sight, but there are many other conditions with which they may be associated The almost constant association of piles with increased intra abdominal tension, as in cirrhosis of the liver, is well known and they also result from portal thrombosis due to porto systemic anastomosis They are therefore, a frequent accompaniment of the dysenteric diseases, the association of external and internal piles with chronic amœbic dysentery has already been referred to (p 167) The following are some of the conditions from which hæmorrhoids must be differentiated

<i>Condition</i>	<i>Means of Differentiation</i>
Per anal condylomata	Positive Wassermann reaction, history
Low rectal polyp	Digital examination
Bilharzial adeno papillomata	Presence of bilharzia eggs in faeces
Amœbic ulceration	<i>E histolytica</i> , free forms or cysts in faeces
Carcinoma of rectum	Digital examination
Polyposis	Digital examination
Granular rectitis	Proctoscopic examination
Rectal prolapse	Appearance of prolapse
Rectal stricture	Digital examination
Anal tuberculosis	Appearance of ulceration and bacteriological examination of discharge

Their usually distinctive and characteristic appearance may be modified by thrombosis ulceration, œdema necrosis, and even gangrene

**External hæmorrhoids** are due to distortion of the veins beneath the skin surrounding the anal margin Recurrent inflammation leads to varicosities causing a redundant condition of the skin and deformity When thrombosed they appear as small bluish tumours beneath the skin and give rise to considerable pain A thrombosed pile usually develops suddenly and gradually increases in size for several hours Often there is no explanation for the sudden appearance of the clot, but it generally occurs when straining at stool Physical exertion, such as running or riding, may bring on an attack The accumulation of moisture round the anus may result in excoriation of the skin covering the clot

Skin tags surrounding the anal margin are the result of fibrosis following some acute inflammation resulting in thrombosis. These tags are composed of skin with a central stroma of connective tissue.

*Internal hæmorrhoids* are varicose tributaries of the middle and superior hæmorrhoidal veins and are situated in the lower 3 or 4 cm of the rectum. Tumours projecting through the anus are classified as internal hæmorrhoids if they are covered by mucous membrane only.

Complications of internal hæmorrhoids are chiefly bleeding and prolapse. Sometimes excoriation of thrombosed piles occurs with sloughing and ulceration. The amount of bleeding varies considerably in different cases. As a rule bleeding occurs together with the passage of stool and the blood oozes from the rectum at the end of the act. Hæmorrhage may however be continuous and occur independently of defæcation. Sometimes it may be so profuse as to threaten the patient's life or continuous bleeding from internal piles may bring about a severe macrocytic anaemia resembling Addisonian anaemia in general appearance. The author has encountered two cases in which a diagnosis of pernicious anaemia had originally been made but where the source of the trouble was traced to bleeding internal piles.

When the piles are ulcerated there may be a discharge of blood stained mucus and it is these which may be mistaken for one or other of the many forms of dysentery.

In making a diagnosis of internal piles a proctoscope should always be employed as they may easily be missed by rectal palpation alone.

## FOREIGN BODIES IN THE RECTUM

Foreign bodies accidentally swallowed may lacerate the mucosa of the rectum on being passed and may in this manner give rise to dysenteric symptoms. Small bones of fish or chicken for instance are often passed by children while adults frequently swallow pins and needles and sometimes screws and tacks held in the mouth. Artificial dentures are sometimes swallowed and may lodge in the rectum. In a similar manner the stones of cherries and plums and the pips of grapes, oranges, melons and other fruits may accumulate and obstruct it. Cases have been recorded in which the foreign bodies have been recovered several months or even several years after being swallowed.

*Foreign bodies introduced into the rectum*.—Remarkable lists have been compiled of foreign bodies which have been introduced through the anus into the rectum either designedly or by accident.

Such bodies have been introduced with the intention of relieving symptoms or curing rectal prolapse hæmorrhoids etc. Insane persons often hide various objects and thieves have been known to conceal gems, coins, keys etc. in this situation. Lockhart Mummery cites the case of a convict at Brest who introduced a box of carpenter's



tools into his rectum. Death in great agony took place seven days later and at post mortem the box measuring six inches by five and weighing twenty two ounces was found, containing several tools, including a screwdriver and a saw. Portions of glass or actual tumblers have been introduced. E. A. Diggins recounts the recovery of a glass from the rectum of a marine engineer in San Francisco. Being conscious of certain symptoms in the rectum he touched something which felt like the rim of a tumbler and broke off part of the edge of the glass leaving a serrated margin. The tumbler was eventually removed in safety by filling it with plaster of Paris.

The following case, in the Albert Dock Hospital in London, was treated by my colleague H. E. Griffiths F.R.C.S., who has kindly permitted me to quote it.

The patient was a boatswain of the P. & O. Lane. On his return from Australia in 1930 he suffered from an acute attack of diarrhoea and during the night he used a tumbler half full of brandy into which he had inserted a raw potato with the idea of checking the condition. Unfortunately the tumbler slipped out of his hand and disappeared into the rectum. He apparently made every effort to recover it without success and for the succeeding five days until the ship docked he was completely obstructed. An X-ray (Plate XXI) was taken as soon as he had been admitted into hospital and it was found that the tumbler was situated completely above the sphincter, which had contracted below it. Great swelling of the mucous membrane had taken place so that it entered the lumen of the tumbler and the rim fitted into a sort of groove between the wall of the rectum and the invaginated mucous membrane. It was thus impossible to approach the actual rim of the tumbler. The abdomen was opened and while an assistant exerted pressure upwards with a sponge holder passed into the rectum the foreign body was manipulated from above. Thus by pushing from below and pulling from above the normal obstetrical process was reversed and the tumbler could be brought up as far as the lower sigmoid. The bowel was opened at this level and the tumbler extracted. The opening in the bowel was repaired by suturing it in layers and in order to give the sigmoid a chance of healing, a temporary colostomy was performed in the upper part of the pelvic colon. The patient made an uninterrupted recovery and after four weeks the colostomy was closed. A few weeks later he returned to his ship and has been at sea ever since.

## Appendices

## APPENDIX I

### THE INTESTINAL PROTOZOA

#### ENTAMOEBA HISTOLYTICA (Schaudinn, 1903)

**Synonyms.**—“*Amœba dysenteriae*” (Councilman and Lafleur, 1891) *Entamœba coli* var *tetragena* (Viereck, 1907) *Entamœba hartmanni* (Prowazek, 1912) *Entamœba dysenteriae* (Councilman and Lafleur, *Entamœba dispar* (Brumpt, 1925)

**Historical.**—(See p 22) It is generally agreed that the amœba first seen by Lösch in 1875 and named by him ‘*Amœba coli*’ corresponds to the generally accepted description of this species. Schaudinn (1903) was apparently the first observer clearly to appreciate the fact that two separate species of amœbæ are found in the intestines of man, one pathogenic and the other not: the former is now known as *E. histolytica*, the latter as *E. coli*.

The fact that *E. histolytica* is to be regarded as essentially a tissue parasite of man was clearly demonstrated by Kartilus in 1885 and 1886, and by Koch in 1887. That infection is brought about by the ingestion of encysted forms was first appreciated by Quincke and Roos in 1893, while from the observations of Uphara (1914), Penfold, Woodcock and Drew (1916), Chatton (1917) and Cutler (1919), it appeared that the secretions in the small intestine cause dissolution of the cyst wall. S. T. Darling (1913) seems to have shown conclusively that intestinal ferments are not essential, for he observed the development of amœbæ in the cysts and their emergence in moist preparations of faeces outside the human body. A. W. Sellards and M. Theiler (1924) showed that *histolytica* cysts hatch when injected intrarectally in kittens, and this finding was confirmed by C. A. Hoare in 1925.

**Habits.**—It appears probable that *E. histolytica*, unlike other intestinal amœbæ, does not habitually feed on bacteria and other intestinal contents, but obtains its nourishment from the living cells and tissues of the intestinal wall. It is probably true that not all the amœbæ (*E. histolytica*) in the intestinal canal actually invade the tissues, but that quite a large proportion apply themselves to the mucous surface of the bowel and cause superficial erosion of the cells without actually burrowing in. In the motile, trophozoite, “vegetative” or tissue invading stage, *E. histolytica* is a relatively large protozoon, usually from 20  $\mu$  to 30  $\mu$  in diameter, even larger forms may occur, and smaller, or *minuta*, stages averaging 10  $\mu$  to 12  $\mu$  in diameter are often present. The cytoplasm of the *E. histolytica* individual has a distinctive refractility which serves to differentiate it from other body cells. There are undoubtedly strains or races which vary in size. Small or *minuta* forms are usually very active, do not contain red blood corpuscles, and are found in diarrhoeic fecal stools. E. Reichenow (1926) believes that the large type, or tissue invading form, lives and feeds on the tissues only, appearing in the lumen of the bowel to encyst, and that the *minuta* really constitutes the precystic form.

C Dobell and M W Jepps (1918) consider that *E. histolytica* is a collective species composed of at least five races, which are distinguishable one from another and which develop on pure lines. They can be differentiated by the size of the cysts they produce. Thus cysts of *E. histolytica* may be found from  $5\ \mu$  to  $20\ \mu$  in diameter. There is no evidence that these different races have any peculiar geographical distribution. Moreover, they remain constant in character within the host, and two may co exist.

I Brumpt (1926) put forward a suggestion which has not been generally accepted to account for the apparently varying degrees of pathogenicity of *E. histolytica*. His explanation, previously offered by Shunamura, is that there exist specific differences between quadrinucleated amoebic cysts. There is, in his opinion, a non pathogenic form of *E. histolytica* which is indistinguishable save for its physiological characteristics. This species he proposed to call *E. dispar*. In 1929 he suggested that man may harbour three species of quadrinucleated cyst amoebae, *E. dispar* with cysts  $10\ \mu$  to  $11\ \mu$  in diameter, *E. hartmanni*, with cysts  $6\ \mu$  to  $10\ \mu$ , and *E. histolytica*. The first two occur in carriers with normal stools and their pathogenicity to kittens is extremely low. It is the presence of these species which explains the incidence of amoebiasis in temperate countries.

J F Hessel (1923) in China investigated the question of the relative virulence of strains of *E. histolytica* from carriers without symptoms and of strains from cases of amoebic dysentery. He was unable to confirm Brumpt's *Entamoeba dispar*.

The question of variations in virulence between different strains of *Entamoeba histolytica* remains unsolved. There can be no doubt that in certain regions, especially in the tropics infections with this parasite are more frequently followed by symptoms of amoebic dysentery than in temperate regions but there is no evidence that this is necessarily due to differences in the virulence of the strains. Moreover those people who suffer in the tropics from the most severe symptoms of amoebic dysentery usually rapidly improve if moved to a temperate region. The favourable effect of a colder climate is to be ascribed to an increased resistance to the infection. Most authorities are convinced that the occurrence of symptoms in amoebiasis depends upon individual resistance to infection rather than upon differences in virulence of different strains of *E. histolytica*.

In the fresh state, i.e., in freshly passed amoebic dysentery stools, especially when warm, the amoebae of *E. histolytica* are very active, they move, or rather flow across the microscope slide in a straight line, suggesting as C Dobell has put it, a 'slug moving at express speed'. At this stage the advancing portion of the body takes the form of a single clear pseudopodium, while the red blood corpuscles which the organism has ingested roll and flow about in the endoplasm as in a mobile fluid. The forms and shapes which an active individual *E. histolytica* may assume during progression may be extremely varied. The pseudopodia may alter in size and position very rapidly, being withdrawn from one situation while being extended at another. In culture these amoebae, as pointed out by J G Thomson and A Robertson (1923), differ considerably from those found in the stools, the shape the organism assumes is ribbon like, with a broad pseudopod extended, of the same breadth as the body, and it is probable that in these circumstances the motion is due to the movements of cytoplasm as a whole.

In contradistinction to *E. histolytica*, other amoebae have a tendency to remain in one place, performing amoeboid movements without progressing materially in any direction.

**Morphology.**—The ectoplasm of *E. histolytica* is normally sharply defined from the endoplasm and is perfectly clear, with a faint greenish transparency. The endoplasm, on the other hand is finely granular and is usually colourless. Sometimes vacuoles, usually round in outline, are present in it, these are true digestive vacuoles resulting from the ingestion and subsequent digestion of foodstuffs. Numerous and irregularly shaped vacuoles are found in degenerated and dying amoebae and in such circumstances may be invaded by bacteria.

Active tissue invading forms usually ingest red blood corpuscles in large numbers and occasionally also other tissue cells. The number of ingested red cells found on examination is usually about ten, but occasionally there may be as many as forty, in all stages of disintegration. They impart a characteristic appearance to the amœba and assist in differentiating it from other intestinal amœbæ, which usually contain bacteria and other debris (Fig 93).

It may be stated categorically that any amœba found in a dysenteric stool and containing red blood corpuscles is *E. histolytica*. Sometimes, when the stools

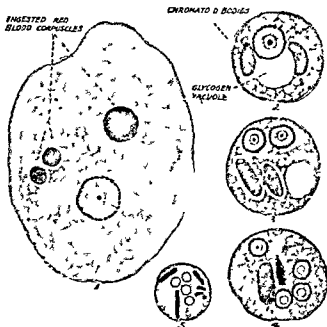


Fig 93 — *Entamoeba histolytica* ( $\times 2,500$ ) (After Dobell)

- 1 Active amœboid form with ingested red blood-corpuscles. 2 Uninucleate cyst.  
3 Binucleate cyst. 4 Quadrinucleate cyst. 5 Quadrinucleate cyst, small race  
6  $6\mu$  to diameter

do not contain blood and are diarrhoeic, the amœbæ do not contain red blood cells, but maintain the morphology characteristic of this species. However, even when the majority do not contain blood cells careful search will usually disclose one or two that do.

Other amœbæ, for instance, *E. coli*, may be present in the blood and mucus stools of bacillary dysentery, but they usually disappear as the disease progresses. On the other hand, the cysts of *E. histolytica* are seldom, if ever, found in a blood and mucus stool. Very soon, within two to six hours after the stool has been passed, according to the temperature, the amœbæ assume abnormal shapes and die out, and this fact has in the past led to much confusion. The amœbæ soon become less active, remaining in one position and sluggishly throwing out large clear pseudopodia, the endoplasm becomes filled with vacuoles, the body invaded with bacteria, the nucleus more prominent, and finally the nucleus breaks up and the organism disintegrates.

The nucleus is so delicate that it is practically invisible in fresh and active forms, but when the organism is fixed and stained it presents a characteristic structure. The nuclear membrane is encrusted with uniform fine granules of chromatin and there is a small dot like central karyosome. Between this karyosome and the nuclear membrane there is a clear area which is devoid of chromatic granules and which is marked by a *linin* network with a radial arrangement. From details such as these the nucleus can be distinguished from that of *Entamoeba coli*.

Multiplication takes place by binary fission and normally occurs in the submucosa of the large intestine. According to C. A. Koford and O. Swezy (1925) there is a modified form of mitosis in which six chromosomes are formed, and it appears that the nuclear membrane persists during the process. Under certain conditions, however, the amoebae become progressively smaller with relatively larger nuclei, they then round up and become inactive—in the *precystic stage*. It was formerly thought that the occurrence of this stage was due to unfavourable external conditions, but it is now, apparently, regarded as a naturally recurring phenomenon in the life cycle, irrespective of environment.

*Cysts*—Cyst formation then takes place, the sole purpose of which according to W. Yorke and A. R. D. Adams (1926), is the transmission of the parasite from one host to another.

Before encystment all the food contained in the amoeba is thrown out. A thin cyst wall is formed, thinner and more transparent than that of *Entamoeba coli*, and the nucleus remains about one third of the diameter of the newly formed cyst. They are then known as *pre cystic forms*.

In the interior of such cyst individuals there are laid down in the cytoplasm one or two massive and deeply staining structures known as *chromatoid bodies*, in *E. histolytica* they are dumbbell like structures with rounded ends thus differing from the acicular needles found, very occasionally in cysts of *E. coli* (Fig. 93, 2 and 3). In some individuals there is a distinct glycogen containing vacuole, but usually the glycogen is diffuse or may even be absent, the early cystic forms of *E. coli* and *Iodamoeba butschlii*, on the other hand, usually possess well marked glycogen vacuoles.

In size, the cysts vary from  $5\mu$  to  $20\mu$  in diameter, thus corresponding to the various small races of *E. histolytica* which have been described. In fresh preparation they are greenish and are especially refractile so that they may easily be picked out with a low power objective slightly out of focus as minute diamond like structures. On staining with Weigert's iodine, the other distinguishing features appear: the thin, round cyst wall, the four characteristic nuclei and the large chromatin bars which gradually disappear as the cysts grow older. Sometimes the cysts contain numerous smaller chromatoid granules. (Plates XXII, 2-5 XXIII 1-4.)

In the fully matured cyst the nucleus is single and corresponds to that seen in the "free" individual but soon it divides, the daughter nuclei separating and taking up positions at opposite poles. A further division then takes place each nucleus dividing into two so that the mature cyst contains four nuclei situated in pairs at the opposite poles of the cyst. The final nuclei are considerably smaller than those of the free or trophozoite individual. Thomson and Robertson have pointed out that frequently there is a curious local thickening of the layer of chromosome granules towards one pole of the nucleus, and that this eccentric thickening, since it does not occur in the nuclei of *E. coli* cysts, may be a useful diagnostic guide.

Yorke and Adams (1927) have shown, from clinical and experimental data, that the quadrinucleate cysts take six to eight hours to develop from the precystic stage in the gut, and that the whole cycle, from the precystic stage through the mature cyst to the excysted quadrinucleate amoebulae, can be passed through in twelve hours. The author has noted that in the human body formation of cysts from precystic stages takes about sixteen hours, as observed in patients in the course of practice. In a recent instance the patient passed in the laboratory at 4 p.m. a stool containing numerous typical active precystic *E. histolytica*, and at 8 a.m. on the following morning a fresh stool showed only typical four nuclear cysts.

**Propagation.**—The cysts of *E. histolytica* leave the body in various stages of development, seldom are more than 50–60 per cent. mature when first passed in the faeces, but it has been observed by W. Yorke and A. R. D. Adams (1926) that immature cysts can complete their development outside the human body. It has been found, also, that these cysts when kept moist and cool and when placed in clear water, may live for a number of weeks, but that they are destroyed rapidly by desiccation or by exposure to high temperatures.

*E. histolytica* cysts begin to die fairly rapidly in faeces kept at laboratory temperature (16–20° C.) for three or four days, and are usually all dead in ten days, the same results are obtained when they are kept at 0° C. in the ice chest. Washed suspensions live longer, especially at freezing point, but even under those conditions, the majority do not live more than three weeks. The cysts can survive a temperature of 45° C. for thirty minutes, but are killed within five minutes at 50° C. (The author sent specimens to Drbohlay in Prague, and from these a kitten was infected successfully ten days later.)

**Resistance to chemicals.**—Yorke and Adams have found that cysts are remarkably resistant to emetine and quinoxyl and relatively so to hydrochloric acid and chlorine. By employing the culture viability test, they found that a 1:2,500 solution of bichloride of mercury killed cysts in thirty minutes; a 1 per cent. solution of carbolic or lysol was equally effective. Formalin, on the other hand, is a comparatively poor agent for their destruction. Potassium permanganate of potash is even less effective. Extended observations by many workers, on the action of substances in water, show that the treatment of water with chlorine cannot be relied upon as a means of exterminating the cysts of *E. histolytica*, because it takes practically a hundred times as much chlorine to kill them as is used in water sterilization, and when so treated it is not potable.

The usually-accepted method of determining the vitality of cysts of *E. histolytica* has been that of W. A. Kuenen and N. H. Swellengrebel (1913)—dead cysts stain with weak watery-eosin solutions, but living cysts do not. Yorke and Adams (1927), however, do not accept this method *in toto*, for they find that not all the cysts which fail to take up the eosin stain may be alive.

The cysts hatch as a rule in the environment in which they are formed, but there seems to be some substance in normal faeces which inhibits their excystment, this being, as Yorke and Adams have pointed out, a natural provision to prevent them from hatching prematurely. They have, however, been found to excyst in both the small and large intestine of cats.

It is a curious fact, and a subject for speculation, that cysts are not formed from active tissue invading amoebae in a liver abscess, or in fact in any secondary amoebic metastatic formation in the human body, nor are they commonly formed in artificially induced laboratory infections in dogs and

cats. It appears that the viability of cysts is dependent, not merely on the amount of available moisture, but also on the prevailing bacterial flora. Kuunen and Swellengrebel (1913) in carrying out a series of experiments, showed for instance, that at a temperature of 27–30° C. cysts kept in water containing bacteria were no longer viable after nine days, but a proportion remained so for twenty nine days at lower temperatures, when the bacterial flora was not excessive. W. C. Boeck (1921) showed further, that cysts stored in distilled water and subjected to thorough washing could survive for 153 or even 211 days.

It is only in the cystic stage that amœbæ can survive outside the body, and it is only by cysts that infection may be spread. Free forms appear to be unable to pass through the human stomach, although C. Dobell and P. P. Laird (1926) found that motile amœbæ could withstand 0.2 per cent hydrochloric acid for thirty minutes.

The amœbæ escape from the cysts (Yorke and Adams) in a suitable medium at body temperature. The quadrinucleated encysted amœba produces a new generation of trophic forms by a complicated series of nuclear and cytoplasmic divisions. The final result is the production of eight uninucleate amœbæ by each quadrinucleate amœba hatching from the cyst. These amœbæ are young trophic amœbæ and not gametes or conjugants. No sexual phenomena of any sort have been observed during the metacyclic stages and the life history of *E. histolytica*, as visible *in vitro* is wholly asexual. (C. Dobell, 1924.)

**Culture.**—The knowledge that active free *E. histolytica* can successfully be cultivated outside the human body we owe to the work of Boeck and Drbohlav (1925). This was first performed on Locke egg medium. Later, Yorke and Adams showed that cultures can readily be obtained by implanting on media such as modified serum medium. Sautet (1926) has shown that the addition of rice or collar starch to the medium greatly assists the growth of the amœbæ, which ingest the granules with avidity.

In cultures of the cysts, the uninucleated and binucleated forms rapidly become quadrinucleated and the nuclei tend to group together towards the centre. The chromatoid bodies form and finally disappear, and so does the glycogen.

The process of excystation is preceded by the withdrawal of the protoplasmic contents from the cyst wall and active pseudopodia like movements are observed within the cyst. Soon a bead of protoplasm is seen protruding from the cyst wall and gradually enlarging by a series of spasmodic movements, until all the contents emerge. The young amœba then moves about trailing the empty cyst envelope behind it. At first the amœbæ are hyaline, but they gradually become vacuolated with the ingestion of bacteria. In cultures made from cysts, large amœbæ are very often found within ten to thirty hours, such forms may contain as many as thirty or forty nuclei. It is not yet known exactly how quadrinucleated amœbæ become uninucleated trophozoites.

The amœbæ, if transferred to a fresh culture every day or two, may be subcultured indefinitely. In cultures they appear to feed on bacteria, although they do not apparently do so in the intestines, if blood corpuscles are inserted into the culture, they devour these also. C. Dobell (1931) has shown that some strains of *E. histolytica* may on culture lose the power of ingesting red blood corpuscles, while others may acquire it. It has been shown that, even after ninety three subcultures kittens can be infected with the cultural forms and a condition may result resembling that produced by injection of maternal



from amœbic dysentery, in a few instances these animals have developed abscesses of the liver. Cyst formation can even be produced and accurately controlled in culture tubes (Dobell).

C Dobell, in a Report of the Medical Research Council for 1931-32, states that the presence of certain bacteria is favourable to the growth of *E. histolytica*, while that of other organisms is harmful, so that special bacteria seem to have a special relation to events in the life cycle. The entamœba is unable to form cysts in culture, unless this particular bacterial species is present, and they are unable to "hatch" in sterile media or in the presence of dead bacteria. These circumstances may shed light on the conditions which cause *E. histolytica*, when present in the lumen of the healthy human intestine, to assume a pathogenic rôle in the tropics.

*Susceptibility of animals to E. histolytica infection*—F Lösch (1875) first succeeded in infecting a dog with *E. histolytica*, but this is more easily performed in young cats, in which Hlava (1887) was apparently the first to produce infection. Kruse and Pasquale (1894) succeeded in infecting cats with amœbæ obtained from liver abscess pus. The disease is usually produced by the injection of dysenteric stools *per anum*, this being the most reliable method. It has been shown that unless cysts are present animals cannot be infected by feeding by the mouth.

*Cat*—In the kitten the infection is usually very severe, so that the whole of the surface of the large intestine is infected with amœbæ, commencing at the lower part of the large intestine where changes in the mucosa are most marked. A W Sellards and L Leiva (1923) have shown that it is at this point that natural stasis occurs. By ligaturing the large intestine of cats at various levels and inoculating material containing amœbæ directly into the cæcum, they demonstrated that the infection commences and is most marked just above the ligature. If the animal survives long enough definite ulcers occur, as in human beings, but usually death takes place from general necrosis of the mucosa. As these observers have shown bacterial invasion of the blood plays a decisive part. Heavily infected cats pass *per anum* a whitish fluid containing broken down cells and enormous numbers of amœbæ. In the less acute stages the stools resemble those of amœbic dysentery in man. Recovery rarely takes place in cats, but when it occurs the infection entirely dies out, no carrier condition being produced as in man. Secondary infection of the liver may take place, leading to liver abscess.

*Guinea pig*—Guinea pigs have been infected by Baetger and Sellards (1914) and later by other workers, infection being brought about by injection *per anum* or by feeding with cysts *per os*. Curiously dysenteric symptoms do not become manifest in these animals, but large tumours develop near the cæcum and are found to consist of hyperplastic tissue containing amœbæ.

*Monkey*—C Dobell and A Bishop (1929) have shown that the entamœba found in monkeys (*Macacus sinicus* and *M. rhesus*) is identical with *E. histolytica* and produces the same pathological effects in these animals as in man. Like man, also, the monkey is amenable to emetine and emetine bismuth iodide treatment. Dobell has also proved (1931) that it is possible to maintain both human and monkey strains indefinitely in these animals and also in cultures *in vitro*.

Amœbic dysentery and amœbic liver abscess may occur in animals in captivity as a natural infection. A Eichhorn and B Gallagher (1916) record a case of dysentery complicated by liver abscess in an orang utan in Manila. In an outbreak in America, spider monkeys (*Ateles ater*) were infected, out

of the nine showing symptoms, only one recovered, and liver abscesses containing amœbæ were found at autopsy in two.

R Hegner, C M Johnson, and R M Stabler (1932) have produced amœbic infections in American monkeys belonging to seven species, including the brown howler monkey, the red spider monkey, and the marmoset. They found in these animals tissue dwelling amœbæ in the tissues of the intestinal wall and *lumen-amœbæ*, living in the lumen of the intestine, but not invading the bowel wall. Injuries of the intestinal wall due to amœbæ were observed in all the twelve infected monkeys examined post mortem. It was found that infection produced by the injection of trophozoites per rectum was more severe and the lesions were more rapidly produced than in oral administration of cysts.

*Dog*—E C Faust (1932) finds that in the dog the site of the lesions, their depth, and their histological structure are comparable with those found in man. The signs of amœbic enteritis in the dog include acute fulminating dysentery, chronic enteritis and convalescent carrier conditions, as well as temporary infections followed by apparent spontaneous recovery. Amœbic hepatitis has been observed in these animals and H F Harris (1901) recorded an amœbic liver abscess.

*Rat*—J F Kessel (1923) claimed that he infected rats with *E histolytica* and that natural infection of these animals with the parasite may occur. The infection artificially produced is chronic and persists for months. The amœbæ from experimental rats, as well as the naturally occurring rat strain (*E histolytica murina*), can give rise to typical symptoms when injected into a kitten. S T Chiang (1925) succeeded in repeating this work and regards the rat as possible reservoir of the infection for man.

**ENTAMOEBA COLI** (Grassi, 1879, Casagrandi and Barbagallo 1895)

**Synonyms**—*Amœba coli* (Grassi 1897) *Entamœba williamsi* (Prowazek, 1911) *Councilmania lafleurii* (Kofoid and Swezy, 1921)

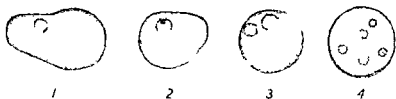
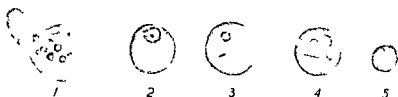
*Entamœba coli* is of interest to the practical physician chiefly because of its close resemblance to *E histolytica*. It is necessary that this protozoon should be recognized in all its stages in order that it may be differentiated from the pathogenic amœba. (Fig 94)

*E coli* lives in the lumen of the human large intestine. It has never been found to invade the tissues. It feeds mostly on the bacteria in the bowel on starch granules, and on yeasts and it may even on occasion, ingest other protozoa such as cysts of *E histolytica*, *Giardia*, and *Isospora hominis*. It does not, like *E histolytica*, ingest red blood corpuscles although K M Lynch (1924) has shown that it can be induced to do so on artificial culture. The free forms vary in size from 10  $\mu$  to 40  $\mu$  in diameter. extremes in size are by no means so common as in *E histolytica*, the majority measuring from 15  $\mu$  to 30  $\mu$ .

There are two protoplasmic layers, as in *E histolytica* but the ectoplasm is not so evident and can only be made out when a pseudopod is extended. In its movement *E coli* is slow, it appears to protrude pseudopodia in all directions when ingesting food material but it does not itself progress, remaining fixed to one spot.

The endoplasm has a close, coarse, granular appearance and is usually vacuolated, it may be very difficult, or almost impossible to distinguish between it and degenerate trophozoites of *E histolytica*.

The nucleus is spherical and vesiculated and possesses an achromatic nuclear membrane usually thicker and more prominent than that of *E*



*P. H. Man on Baker del*

**HUMAN INTESTINAL PROTOZOA (unstained)**

**PLATE XXII**

## PLATES XXII AND XXIII

### INTESTINAL PROTOZOA

#### Row A. *Entamoeba histolytica* (Unstained )

- 1 —Active vegetative form with ingested red blood corpuscles granular endoplasm and clear ectoplasm
- 2.—Precystic form Note large nucleus with central karyosome
- 3 —Immature cyst with two nuclei and contained chromatoid rods
- 4.—Mature cyst with four nuclei, vacuole and chromatoid rods
- 5 —Unnucleated cyst of the minuta stage

#### Row A<sub>1</sub> *Entamoeba histolytica* (Stained Weigert's Iodine )

- 1 —Precystic form. Note diffuse iodine-staining substance
- 2 —Immature cyst with two nuclei and chromidial rods
- 3 —Mature cyst with four nuclei iodine vacuoles and chromidial rods
- 4 —Quadrinucleated cyst of the minuta stage

#### Row B *Entamoeba coli* (Unstained )

- 1 —Active vegetative form with characteristic nucleus blunt pseudopodia and protoplasmic vacuoles with food material
- 2 —Precystic form with characteristic nucleus
- 3 —Immature stage with two nuclei and vacuole
- 4 —Mature cyst with eight nuclei

#### Row B<sub>1</sub> *Entamoeba coli* (Stained Weigert's Iodine )

- 1 —Active vegetative form with vacuoles and ingested food material
- 2.—Precystic form
- 3 —Immature cyst with two nuclei and vacuole
- 4 —Mature cyst with eight nuclei

#### Row C *Endolimax nana* (Unstained.)

- 1 —Active vegetative form with one nucleus and many small vacuoles
- 2 —Mature cyst with four nuclei

#### *Iodamoeba butschlii* (Unstained )

- 3 —Active vegetative form with one nucleus and large vacuole
- 4 —Mature cyst with one nucleus and large vacuole

(Continued overleaf )

# PLATES XXII AND XXIII

## INTESTINAL PROTOZOA (Continued)

### Row C<sub>1</sub> *Endolimax nana* (Stained Weigert's Iodine)

- 1.—Active vegetative form with one nucleus and protoplasmic granules
- 2.—Mature cyst with four characteristic nuclei and iodine-staining substance

### *Iodamoeba butschlii*. (Stained Weigert's Iodine)

- 1.—Active vegetative form with one nucleus and iodine-staining vacuol
- 2.—Mature cyst with one nucleus and iodine-staining vacuole

### Row D *Giardia intestinalis* (Unstained)

- 1.—Active form with sucking disc
- 2.—Active form (side view)
- 3.—Cyst with two dividing nuclei
- 4.—Four nucleated cyst (end on view)

### Row D<sub>1</sub> *Giardia intestinalis* (Stained Weigert's Iodine)

- 1.—Active form with sucking disc
- 2.—Active form (side view)
- 3.—Cyst with two dividing nuclei
- 4.—Four nucleated cyst (end on view)

### Row E *Trichomonas hominis* (Unstained)

- 1.—Active form with undulating membrane and supporting rod

### *Chilomastix mesnili* (Unstained)

- 2.—Active form with peristome and contained flagellum
- 3.—Pear-shaped cyst of above
- 4 5 6.—Various forms of *Blastocystis hominis*

### Row E<sub>1</sub> *Trichomonas hominis* (Stained Weigert's Iodine)

- 1.—Active form with undulating membrane and ingested red blood corpuscles the latter is an occasional occurrence

### *Chilomastix mesnili* (Stained Weigert's Iodine)

- 2.—Degenerated form as it commonly appears when acted upon by iodine.
- 3.—Pear-shaped cyst of above with nucleus and peristome
- 4 5 6.—Various forms of *Blastocystis hominis*

A/



1



2



3



4

B/



1



2



3



4

C/



1



2



3



4

D/



1



2



3



4

E/



1



2



3



4



5



6

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# **HUMAN INTESTINAL PROTOZOA** (Stained with Weigert's iodine)

*histolytica* The nucleus is filled with a fluid through which a *linear* reticulum is spread. The *chromatin* of the nuclear membrane occurs in large masses and is more irregular than that of the *E. histolytica* nucleus. The *karyosome* is placed excentrically within the nucleus and in stained preparations is surrounded by a clear space termed a *halo*.

Multiplication in *E. coli* is by binary fission and this process appears to be initiated in the *karyosome*. The nucleus divides by a modified mitotic process into two daughter nuclei, each of which possesses the same characters as the parent nucleus.

Propagation of *E. coli* is by means of resistant cysts. Before encystment

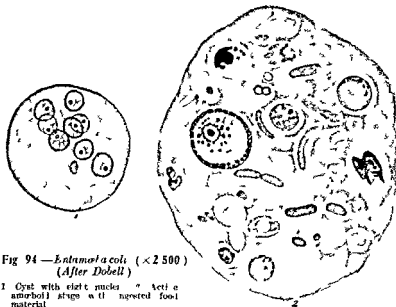


Fig 94 — *Entamoeba coli* ( $\times 2,500$ )  
(After Dobell)

1 Cyst with eight nuclei. 2 Active amoeboid stage with ingested food material.

the vegetative amœbæ become smaller and void any foodstuffs they may have ingested. They are now known as *pre-cystic* amœbæ which are sluggish and round. In a short time by secreting a cyst wall as a rule distinctly thicker than that of *E. histolytica*, they become *cysts* which are usually larger than those of the pathogenic amœba. They vary in diameter from  $10\ \mu$  to  $30\ \mu$  but usually measure  $15\ \mu$  to  $20\ \mu$ ; larger forms however may occur. The type of cyst most commonly found in the stools is one which contains eight nuclei.

The newly formed cyst contains a considerable amount of glycogen, acicular shaped chromatoid bodies and a nucleus which has the characters of the free form. This nucleus soon divides into two then into four, and finally into eight; very occasionally cysts are found which contain as many as sixteen. The contained glycogen can be demonstrated when stained with iodine solution. As a rule, the amount of this substance is greater than in *E. histolytica*, but it tends to disappear more rapidly. The chromatoid bodies are best seen in fresh unstained specimens; they are threadlike with sharp pointed acicular ends and like the glycogen they disappear rapidly.

from the cysts. Occasionally vacuoles appear round the periphery of the cyst while the cytoplasm with contained nuclei occupies the centre (Plates XXII, XXIII, B, 1-4)

*E. coli* can be cultivated, but with considerable difficulty, on the medium of Boeck and Drbohlav (1925). These workers, and also J. G. Thomson and A. Robertson, have managed to keep strains alive for a considerable period.

**ENDOLIMAX NANA** (Wenyon and O'Connor, 1917, Brug, 1918)

**Synonyms.**—*Entamoeba nana* (Wenyon and O'Connor, 1917) *Endolimax intestinalis* (Kuenen and Swellengrebel, 1917)

This is one of the most common protozoa of the human intestinal canal, and is certainly non pathogenic. It occurs in quite a large proportion of the normal human population, a percentage of 2.4 being found by J. R. Matthews

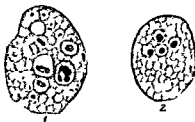


Fig. 95 — *Endolimax nana* ( $\times 2,500$ )  
(After Dobell)

1 Active ameboid form 2 Quadrinucleate  
mature cyst.

and A. M. Smith (1919) in English adult civilians and 27.8 by Koford and Swezy (1920) in home service troops in the United States. Owing, doubtless, to its small size and delicate structure, a great many infections are missed. It is chiefly important in that it is likely to be mistaken for the small race of *E. histolytica*, this applies mainly to the small quadrinucleated cysts (Plates XXII, XXIII, C, 1-2)

In its free state *E. nana* measures from  $6\ \mu$  to  $12\ \mu$  in diameter. It is usually seen to move sluggishly, but it is more active on a warm stage, its movements are more like those of *E. coli* than those of *E. histolytica*. The organism exists in the faeces as a commensal, and ingests bacteria as well as other gut contents, which can be seen inside the numerous vacuoles. The nucleus is vesicular and spherical and is separated from the cytoplasm by a definite nuclear membrane. All the chromatin is collected into a large, irregularly shaped karyosome which is usually eccentrically placed within the nucleus, there is no peripheral or intermediate chromatin. (Fig. 95)

The free forms of *E. nana* are frequently parasitized by *sphaerita*, an organism composed of highly refractile round globules.

**Precystic forms**, the cytoplasm of which is free from inclusions, form uninucleated cysts which are typically oval in outline and contain glycogen in varying quantities. No chromatoid bodies occur, but granules may be observed. When mature, the cyst contains four nuclei which are usually grouped together at one pole of the cyst. The nuclear characters are similar to those of the free forms, but they are smaller. Cysts vary from  $8\ \mu$  to  $10\ \mu$  in length by about half that in breadth and are usually very numerous.



*Endolimax nana* has been cultured with difficulty, on Boeck and Drbohlav egg medium by J G Thomson and A Robertson (1925)

### IODAMEBA BUTSCHLI (Prowazek 1912 Dobell 1919)

**Synonym.**—*Iodamaba wenyoni* (Brumpt 1921)

This organism occurs as a harmless coprozoic commensal in man and closely allied organisms are found in the pig and in monkeys. It is now known to be a comparatively common infection. Matthews and Smith found 0.4 per cent in Army recruits and 0.18 per cent in children under twelve in England while Wenyon and O'Connor found 14 per cent of the prisoners in Hadra prison Alexandria infected. C Dobell (1919) found that *I butschli* is often associated in man with infections of *F histolytica*, *E coli* and *E nana*.

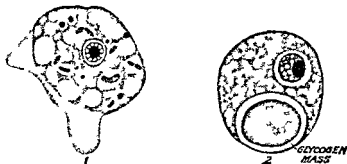


Fig 96 —*Iodamaba butschli* ( $\times 2500$ ) (After Dobell)

1 Active amoeboid form with ingested microorganisms. Mature cyst containing large glycogen mass.

A remarkable feature of this infection in man is the immense number of cysts which are passed without the ascertainable presence of free forms. (Plates XXII XXIII, C 3-4)

The majority of the free forms measure between  $9\mu$  and  $13\mu$  in diameter though Dobell states that individuals may attain  $17\mu$  to  $20\mu$  and others may be as small as  $5\mu$ . The movements are very sluggish like those of *E coli*. The cytoplasm of the free form is divisible into an ectoplasm and endoplasm, this being specially noticeable in the cultural forms which have been obtained. As a rule the cytoplasm contains numerous vacuoles and ingested bacteria. The nucleus is large and vesicular and has all the nuclear chromatin collected together in a large karyosome. Surrounding this karyosome is a zone of lightly staining granules and some filaments of *linin*. (Fig 96)

The cysts of *I butschli* which measure  $7\mu$  to  $17\mu$  are easily recognized. They exhibit irregular oval or spherical outlines but when stained by Weigert's iodine the glycogen which is usually abundant, is defined as a brown mass and the margins of the vacuole in which the glycogen is situated are clearly defined. This gives the cysts such a characteristic and striking appearance that before their true nature was realized they were known as 'iodine cysts'. When the cysts are fully mature the glycogen tends to disappear.

Most cysts contain only one nucleus though cysts with two nuclei are not uncommon in some infections. In this amoeba there is apparently no definite

precystic stage, or at any rate a reduction in the size of the organism does not occur. All foodstuffs are removed from the cytoplasm, which now becomes clear, transparent, and finely granular in appearance. The cyst wall is secreted and soon glycogen appears to be produced.

### DILTAMOEBA FRAGILIS (Jepps and Dobell, 1918)

#### Synonym.—*Histomonas fragilis*

This amoeba is seldom found in faeces and is by far the least frequent of all the human intestinal amoebae. The reason advanced for its apparent scarcity is that it is highly susceptible to small variations in temperature and, directly the faeces become chilled on passing out from the body, becomes spherical and motionless, thus escaping detection.

*D. fragilis* is comparatively small in size, from 3  $\mu$  to 12  $\mu$  in diameter. The cytoplasm is sharply differentiated into ectoplasm and granular endoplasm (Fig. 97). The pseudopodia are active and tend to be conical in outline; are in fact leaf-like (Dobell) and they may give rise to secondary smaller pseudopodia. The endoplasm is finely granular and may be vacuolated and contain bacteria and ingested food material. The majority



Fig. 97.—*Dientamoeba fragilis* uninucleate and binucleate forms ( $\times 2,500$ ) (After Dobell)

of the free forms are binucleate and have the nuclei situated near to one another. It is thought probable that these binucleate amoebae are the mature individuals which on division give rise to uninucleate forms. The nucleus is a fine structure and has an achromatic nuclear membrane. The nuclear chromatin is arranged in a ring of granules, four, five or six in number, midway between the central point of the nucleus and the nuclear membrane. So far no workers have described encysted forms.

From his intimate studies of *E. fragilis* in monkeys, C. Dobell (1940) has now modified his views on its morphology. As seen in culture, the forms possess two nuclei connected by a thread (*centrodesmose*) resembling the flagellate *Histomonas meleagridis*, the cause of blackhead in turkeys. This normally lives as a flagellate in the cecum but can invade the liver, where it assumes the flagellate amoeboid form.

J. G. Thomson and A. Robertson have found that this organism can be cultivated on the egg medium of Boeck and Drbohlav, but that it is rapidly overgrown by the yeast-like *Blastocystis*.

### GIARDIA INTESTINALIS (Lambl, 1858, Alexeieff, 1914)

**Synonyms.**—*Lamblia intestinalis* (Lambl, Blanchard, 1855) *Giardia lamblia* (Stiles, 1910)

The members of the genus *Giardia* are characterized by having a body which resembles a pear split longitudinally. The dorsal surface is convex, while the ventral surface is flat, and the body ends in a posterior tapering

tail which is a flexible structure that can be turned up over the convex dorsal surface. The remainder of the body is rigid. On the ventral surface there is a sucking disc, almost circular in outline save for a posterior orientation which is provided with a raised edge. By means of this disc the flagellate is able to rest attached to the surface epithelium of the bowel. It has four pairs of flagella symmetrically arranged and two nuclei one lying on each

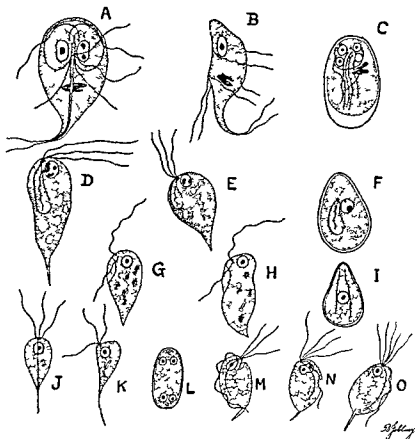


Fig 98—The flagellates of the human intestine ( $\times 2000$ )

(After Henry by permission)

A, C *Giardia intestinalis* free and encysted forms. D, E, F, G, H, I, M, N, O *Entamoeba histolytica* free and encysted forms. J, K, L, M, N, O *Trichomonas hominis* free and encysted forms. M, N, O *Trichomonas hominis* forms with three, four and five flagella.

side of the middle line of the body. When swimming the active form sways from side to side like a flat fish passing through a liquid medium. The internal structure is somewhat complicated. (Fig 98 A-C)

Reproduction takes place by binary fission and is usually accomplished within an ovoid which first forms round the anterior end of the body and expanding backwards gradually encloses the tail which is finally retracted

within the cyst wall. In a recently encysted *Giardia* both the flagella and the tail may be seen moving within the cyst. The parasite divides inside the cyst so that eventually two separate individuals, with two sets of nuclei and accompanying organs, lie inside, therefore on superficial examination it may be mistaken for a four nucleated cyst. (Plates XXII and XXIII, D, 1-4.)

The cysts of *Giardia* persist in the stools for years, the numbers varying considerably from time to time. Cases have been observed by the author in which cysts have persisted continuously for seven years.

The human species *Giardia intestinalis*, is a common intestinal parasite of man and has a world wide distribution. As it lives in the upper part of the small intestine, its habits differ considerably from those of the other intestinal protozoa which inhabit the large bowel.

During the last seventeen years many observers have found large numbers of these flagellates in the duodenal juices removed by means of the duodenal tube, and it has also been seen in the bile obtained at operation by duodenobiliary drainage, but there appears to be no evidence that it can live for any length of time in the gall bladder. Encysted forms are commonly seen in the stools of infected persons, but it is only in diarrhoeic conditions that the free active forms occur. When occurring in stools, in the active form, they are often found in numbers in flakes of mucus swaying about packed together, like minnows in a stream. The vegetative form is from  $9.25\ \mu$  to  $20.24\ \mu$  in length (average  $13.7\ \mu$ ) and in breadth from  $5\ \mu$  to  $10.25\ \mu$  (average  $7.46\ \mu$ ). The cysts vary in length from  $8\ \mu$  to  $14\ \mu$  (average  $10.7\ \mu$ ) and in breadth from  $6\ \mu$  to  $10\ \mu$  (average  $7.47\ \mu$ ). (Fig 98, C.) It appears to be more common in the tropics than in temperate countries, but undoubtedly it is spread over the whole world. C. M. Wenyon and F. W. O'Connor in 1917 found that it was present in 41 to 16 per cent. of normal individuals in Egypt, while C. Dobell estimated that 18 to 27 per cent. of the artisan population of the British Isles harboured this flagellate. W. C. Boeck and C. W. Stiles (1923) found it in 48.1 per cent. of school children in America.

#### TRICHOMONAS HOMINIS (Davaine, 1860)

**Synonyms.**—*Cercomonas hominis* (Davaine 1860) *Trichomonas intestinalis* (Leuckart, 1879)

*T. hominis* inhabits the human intestine, where, probably, it is quite harmless. It is usually rounded or oval, but it can adopt a great variety of shapes. It measures  $10\ \mu$  to  $15\ \mu$  in length by  $7\ \mu$  to  $10\ \mu$  in breadth (Plates XXII, XXIII, E, 1).

At the anterior end of the parasite there is a mass which stains deeply and is a congregation of blepharoplasts from which arise flagella, usually four in number. The nucleus situated at the anterior end, is round and vesicular. There is also a thick strong lateral flagellum which, passing backwards from the blepharoplasts, serves as the outer margin of a wide undulating membrane. At the further end of the parasite it becomes free for a short distance. A small aperture near the anterior end represents the mouth, or cytostome. Within the body of the parasite, passing from the blepharoplast to the posterior end, is a short supporting skeletal structure, or axostyle which, in some instances, appears to curve round the nucleus. The cytoplasm is vacuolated and may contain bacteria. As in other intestinal flagellates, the movements of *T. hominis* are most characteristic. The four anterior flagella usually work together in a wide sweeping fashion so that the parasite progresses forward in a spasmodic manner. (Fig 98, M-O.)

According to the number of free flagella (three, four or five), three varieties of *Trichomonas* have been described

Multiplication takes place by binary fission, but no cysts of this organism are known. Cultivation can easily be effected on Boeck and Drbohlav's Locke egg medium

#### CHILOMASTIX MESNILI (Wenyon, Alexeieff, 1910)

**Synonym.**—*Tetramitus mesnili* (Wenyon, Alexeieff, 1910)

*Ch. mesnili* is a pear shaped organism measuring  $10\ \mu$  to  $15\ \mu$ , with a blunt, rounded anterior and a tapering posterior extremity, the latter being prolonged, usually, into a tail or caudal process. At the anterior end there is a groove which passes down the body for one third or half its length before opening into the cytoplasm. This constitutes its mouth, or cytostomal cleft, in which is placed a flagellum which moves rhythmically and creates a current along the grooves which wafts food particles to the opening of the mouth proper. This food material consists of cocci and bacilli which are engulfed along with fluid. The nucleus is placed close to the anterior margin of the body and on its outer aspect, at the most anterior part, is a blepharoplast from which the three anterior flagella arise. The movements consist of forward progression accompanied by a rotation of the body on its own axis. On each side of the mouth is a stiff and fine fibril which acts as a support. (Plates XXII, XXIII, E, 2, 3)

Multiplication is by binary fission in the long axis of the parasite, which produces characteristic, lemon shaped cysts measuring  $7\ \mu$  to  $9\ \mu$  in length. The mature cyst contains a single nucleus of much the same appearance as that of the trophozoite. (Fig 98, D-F)

#### TRICERCOMONAS INTESTINALIS (Wenyon and O Connor, 1917)

**Synonym.**—*Enteromonas hominis* (Fonseca, 1915)

This parasite was discovered by Wenyon and O Connor in 1917 in Alexandria and it has since been frequently found, mostly in Malaya as pointed out by J G Thomson and A Robertson who, in 1925, succeeded in cultivating the organism on Locke egg medium

*T. intestinalis* is a minute, very active flagellate, almost pyriform in shape measuring  $4\ \mu$  to  $10\ \mu$  in length by  $3\ \mu$  to  $6\ \mu$  in breadth. The anterior end is rounded, but the posterior is drawn out to a fine point. One side is convex, the other flattened and possibly grooved longitudinally. The nucleus is single and vesicular, measuring  $1.5\ \mu$  to  $2\ \mu$  in diameter, with a large centrally placed karyosome. The blepharoplasts are situated near the nucleus in one of them three flagella of equal length arise and are directed forwards. The other blepharoplast is situated near the flattened side of the body and from this arises the fourth flagellum which runs to the posterior extremity of the body, ending as a terminal lash. When the movement is studied in living organisms the combined result of the flagellar lashings imparts a hovering effect.

The cysts are small and closely simulate fungus spores. They are usually oval with a distinct cyst wall, and included within them are certain rounded and highly refractile bodies which stain brown with iodine. (Fig 98, J-L)

#### EMBADOMONAS INTESTINALIS (Wenyon and O Connor, 1917)

**Synonym.**—*Waskia intestinalis* (Wenyon and O Connor, 1917)

*E. intestinalis* was originally discovered by C M Wenyon and F W

O Connor in Egypt in 1917 and has since been found to be widespread. It is a small flagellate  $5\mu$  in length by  $3\mu$  in breadth, which, when fresh is very active. It is pyriform in shape, with a blunt, rounded anterior end, and tapers to a point posteriorly. When viewed sideways it has been described as bird like. It possesses two flagella: one, directed anteriorly, is long and thin and is the chief means of propulsion; the other, projecting laterally from the cytostome, is much stouter. The combined action of these flagella produces a peculiar jerking movement of the body. The cytostome faces in a lateral direction so that it aids the ingestion of bacteria. (Fig 98, G 1)

The nucleus is spherical and vesicular and possesses a distinct nuclear membrane and a large central karyosome. Two blepharoplasts from which the flagella originate are applied to the nuclear membrane.

The cysts which measure  $4-9\mu$  by  $2-3\mu$  are minute pear shaped bodies in which it is extremely difficult to detect any internal structure.

### BALANTIDIUM COLI (Malmsten, Stein, 1862)

**Synonym** —*Paramacium coli* (Malmsten 1857)

*Balantidium coli* is the shape of an egg or a pear, and measures  $50-80\mu$  in length by  $50-70\mu$  in width, being usually about one and a quarter times as long as broad. In exceptional cases, however, it may be  $200\mu$  in length and  $90\mu$  in breadth. The anterior end is pointed, the posterior rounded or blunt (Fig 99). At the anterior extremity and situated somewhat obliquely is a depression known as the peristome, which marks the ventral surface of the ciliate, with constant movement this opening varies in shape and it may appear as a longitudinal groove or slit. It is lined by numbers of cilia, and the whole body of the parasite is covered with these organs arranged in longitudinal rows in grooves between the ectoplasmic regions. Individual cilia are  $4-6\mu$  in length; those in the neighbourhood of the cytostome or adoral zones measuring  $8-12\mu$ .

A sausage shaped micronucleus lies more or less transversely in the middle of the body, while close above it in a slight depression is situated the small macronucleus. There are two contractile vacuoles: one at the posterior end and the other near the centre of the body. Finally an anal aperture is present beneath which lies clear ectoplasm; the condition of the endoplasm varying with the stage of digestion. Reproduction takes place by transverse fission after the division of the two nuclei. During this process the body becomes contracted and hour glass shaped, the cytostome remains within the anterior wall and a new mouth cavity is formed. Multiplication in this manner has been observed to take place in the lumen of the bowel and in the tissues where the parasite has penetrated the mucous membrane. Conjugating stages have been observed, according to Brumpt, the two ciliates become attached to one another by their peristomes and enclosed in a cyst and it is supposed that in its formation fusion of the bodies of the two ciliates takes place. More frequently a single ciliate becomes encysted, during this process it becomes nearly spherical creating around itself a cyst wall which consists of two distinct layers. This cyst appears to be a purely protective structure for no multiplication has been seen within it. Individual cysts measure from  $50-60\mu$  in length and slightly less in breadth. They are voided in the feces and undoubtedly are instrumental in spreading infection.

According to the majority of authors these ciliates multiply most frequently in the cecum or appendix, in neutral or alkaline media. E. C. Nelson has

succeeded in infecting rats with balantidia from the chimpanzee by introducing them directly into the stomach

*Cultivation*—*Balantidium* has been cultivated outside the body by H P Barret and N Warbrough (1921) employing as a medium a mixture of

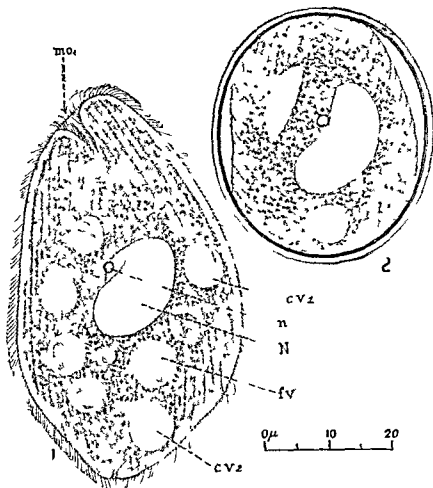


Fig 99—*Balantidium coli* ( $\times 1200$ ) (After Dobell by permission of Medical Research Council Report No 51)

1 Living animal n macronucleus n micronucleus cv1 anter or contractile vacuole cv2 poster or contractile vacuole fv food vacuole mo mouth

2 Encysted form showing nucleus poster or contractile vacuole and remains of cilia

inactivated human serum with 0.5 per cent of salt solution in the proportion of 1 in 16 they have been able to cultivate it by subinoculation for fifty-four days

### BLASTOCYSTIS HOMINIS

*Blastocystis hominis* (Plates XXII XXIII E 2-6) a yeast-like organism which may simulate the encysted stage of an amoeba is very common

in the faeces. It multiplies by gemmation and can be recognized on microscopic examination especially in iodine preparations. It has an irregular oval or bilobed shape. There is a large central vacuole which does not stain with iodine, but there are prominent iodophilic granules in the periphery of the cell which give it a rough resemblance to a double sided signet ring. These organisms vary a good deal in size, from 2-15  $\mu$  in diameter. They are found most commonly in dysenteric and sprue stools, but are of no pathological importance.

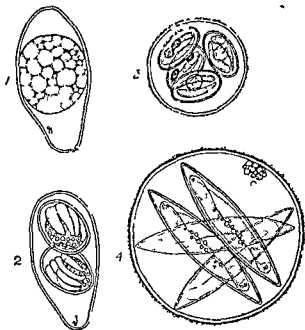


Fig. 100.—Oocysts of coccidia found in human faeces ( $\times 1000$ )  
(After Dobell)

1 *Isospora hominis*, undeveloped cyst. 2 Fully developed sporozoites of same. 3 *Isospora* *disseminata*, fully developed oocyst and spores. 4 *Isospora* *parvula*, fully developed oocyst and spores.

## COCCIDIA

The coccidia are intracellular protozoa which inhabit the cells of the intestinal canal and liver of vertebrates. Their life history differs from that of the amoebae in that they exhibit an alternation of generations in which an asexual cycle—schizogony,—alternates with a sexual cycle—sporogony. In the latter cycle a single zygote becomes encysted as an oocyst, and eventually produces a number of sporozoites which are included in masses in smaller cysts (sporocysts). The young parasites—or sporozoites—are liberated from a sporocyst in the intestinal tract, they then penetrate epithelial cells and grow into large schizonts characterized by a large vesicular nucleus and a karyosome. When full grown the nucleus divides by repeated



fission till a number of daughter nuclei are produced. The schizont now divides into as many merozoites as there are nuclei. The cell then bursts and the merozoites are set free, enter other cells and develop either into schizonts again or into gametocytes. These later are sexually differentiated.

Several instances are recorded of the finding in the human liver of oöcysts of coccidia which resemble those of *Eimeria stiedæ* of the rabbit, and oöcysts of the different species of coccidia are occasionally found in human faeces. When so found, coccidia of the genus *Eimeria* pass unchanged through the intestinal canal, they are actually parasites of the roe of fish, e.g. herring or sprat, and are unaffected by the processes of digestion. Two species are known as *Eimeria clupearum* (*E. wenyon*) and *Eimeria sardinæ* (*E. oxyispora*) respectively. Attention is here drawn to them because they were for some time considered to be human parasites. (Fig 100, 3, 4.)

One species only is parasitic in man though it is not seriously pathogenic.

***Isospora hominis*** (Railliet and Lucet, 1901)

*Synonym* —*Isospora belli* (Wenyon, 1923) \*

As mentioned on p. 266, over 150 cases of infection with this organism have now been described in man most of them hailing from the eastern Mediterranean. The schizogonic cycle of development in the human intestine is not known. The oöcysts are elongated and oval with tapering extremities and vary in length from 18 to 33 $\mu$  and in breadth from 12.5 to 16 $\mu$ . They have a clear and colourless oocyst wall. They are usually discharged in the faeces with the zygote in an unsegmented condition, but occasionally after segmentation into sporoblasts. In the faeces outside the body the zygote segments to form two ovoid sporoblasts which soon become enclosed in sporocysts, each containing four sporozoites. (Fig 100, 1, 2.)

\* C. A. Hoare now considers *I. hominis* and *I. belli* distinct species: the former being probably a dog parasite accidental in man while the latter is a human species parasitic in the epithelium of the small intestine.

## APPENDIX II

### LABORATORY METHODS

#### EXAMINATION OF FÆCES

**General.**—It cannot be over emphasized that in examination of fæces, whether for the presence of protozoa or of bacteria, the sooner the specimen is examined in the laboratory the more accurate and convincing will be the pathologist's report. Indeed, whenever possible, the patient should pass a specimen into a suitable receptacle in the laboratory so that it may be examined while still warm. The patient is provided with a separate vessel for urination, to prevent contamination. The receptacle into which the stool is passed must be clean and free from disinfectants. From a bed case the stool should be sent to the laboratory as speedily as possible.

*Forwarding samples for examination.*—If the patient resides in the town in which the laboratory is situated, a sample of stool, enclosed in a suitable container, may be sent by messenger. In England, stringent Post Office regulations govern the forwarding of pathological material by post. The familiar faeces tube—a glass tube into the cork of which a metal spoon is fixed—must be enclosed in a wooden case and prevented from jolting by picking the top with cotton wool. After suitable wrapping, the parcel is labelled 'Pathological Specimen,' 'Fragile,' 'With great care.' The specimen should be posted late at night or in the early morning and should be examined immediately it reaches the laboratory.

In the tropics, if the specimen has to come a long distance, it is sent by native runner. Various devices have been utilized for keeping the specimen 'fresh' and perhaps the best method for the detection of amœbæ in a suspected case is to put the tube containing the sample into a Thermos flask filled with water at 36° C. for possible bacillary dysentery, fæces may be emulsified with a double volume of 30 per cent glycerin in 0.6 per cent saline solution or even better, with an equal volume of  $\frac{1}{33}$  NaOH solution which, by rendering the medium alkaline, conserves vitality of the organisms for a longer period.

*Disposal of infected material.*—For the disposal of fæces tubes after examination of the contents an enamel bucket provided with a lid is filled three quarters full with 3 per cent Lysol, this having been found preferable to other 'sticky' disinfectants. Into this bucket the tubes are dropped after removal of the corks. They are left till the bucket is full, and after a few days it will be found that all the faecal contents have softened and can easily be removed from the tubes. The fluid material is then poured off and the tubes rinsed in warm water. They are then transferred to a saucepan containing warm water in which soap powder has been dissolved and are boiled for ten minutes. They are next rinsed in clean water, washed in 10 per cent hydrochloric acid in water, rinsed three times in running water and inverted on a tray to drain.

## MACROSCOPICAL EXAMINATION OF FÆCES

Considerable aid in determining the cause of a diarrhoeic condition may often be obtained by careful macroscopical examination of fæces, and where possible the whole stool should be inspected. The bacillary dysentery stool may often be composed of fluid blood and mucus, while the amœbic usually consists of thick blood and mucus intermingled with fæces. It must be realized, however, that the stool of convalescing bacillary dysentery may simulate that of amœbic, or balantidial dysentery, intestinal bilharziasis, or ulcerative colitis.

The consistency, colour, smell, and presence or absence of blood or mucus should be noted. A fresh bacillary dysentery stool gives off the odour of spermin or freshly laundered linen, while the amœbic is usually offensive. The sprue stool is bulky and may be composed of thick rolls not unlike farm house butter, or semi solid material resembling cream. It has a characteristic sour odour, whereas the sprue like stool which is sometimes seen following an attack of Sonne dysentery and that of celiac disease in children are usually more offensive. The liquid or semi solid stool of pancreatitis smells like Cheshire cheese. The characteristic stool in mucous colitis contains thick "strings" of mucus, that of cholera is odourless and resembles "rice water". Stools of the typhoid group may contain a small quantity of blood and mucus and have a characteristic smell not unlike that of butcher's meat, and when fluid resemble pea soup. In intestinal tuberculosis the stool usually consists of greenish fæces containing much mucus with little blood, and is very offensive, when associated with intestinal polyp it often bears a resemblance to sputum. The stools of rectal carcinoma and of ulcerative colitis are very similar. They may resemble amœbic dysentery and are very offensive. In bleeding piles bright red blood is usually found in the terminal portions of the stool. In a heavy *Guardia* (*Lambia*) infection the stool is not usually offensive and consists mostly of thin mucus intermingled with liquid pale fæces, those associated with other flagellate infections are gelatinous, watery, and odouriferous.

In Table XX an attempt has been made to tabulate the characteristic stools of different conditions. It must, however, be understood that the various points stressed are by no means constant, for there are many factors, such as foods and drugs, that alter the appearance of fæces. Nevertheless an experience of over a quarter of a century in examination of stools has convinced the author that in many instances a stool can be classified to a great extent on the naked eye appearances and odour.

## MICROSCOPICAL EXAMINATION OF FÆCES

If the stool to be examined contains blood and mucus a small portion is removed by the aid of a match stick porcupine quill or platinum loop, and placed in the centre of a clean slide, a cover glass is placed on the mass and gently pressed down. Examination should be made first by means of the  $\frac{3}{8}$  in objective to search for helminthic ova then with the  $\frac{1}{4}$  in. The iris diaphragm should be racked down about half an inch so that the light is not too strong. A note should be made of the type of cells observed (see p. 83).

If free amœbæ are seen, the following points should be noted. cytoplasm

Disease	Macroscopically	Odour
PANCREATITIS	Bulky, yellowish-white, liquid or semi solid faeces which "set" in half an hour after passage. No blood or mucus.	"Cheesy"
CELIAC DISEASE AND IDIOPATHIC STEATORRHOEA	Liquid or semi solid, bulky, yellowish white faeces. No blood or mucus.	Very offensive
SPRUE	Bulky, fermenting, yellowish-white, liquid faeces or soft solid faeces like rolls of farmhouse butter. No blood or mucus.	Sour
BACILLARY DYSENTERY	Thin blood and mucus or blood and mucus with greenish liquid faeces.	Not offensive, like freshly laundered linen.
TYPHOID FEVER AND PARATYPHOID	Liquid, brown, 'pea soup' faeces sometimes with little thin blood and mucus.	Very offensive, like butcher's meat.
CHOLERA	Thin, watery, 'rice-water' stools. No blood or mucus.	Odourless
AMEBIC DYSENTERY	Thin blood and mucus intermingled with normal or liquid faeces. Often only minute quantity of blood and mucus.	Offensive
BALANTIDIAL DYSENTERY	Liquid, brown faeces intermingled with blood and mucus.	Very offensive
GIARDIASIS	Mostly mucus, or liquid faeces with considerable amount of thin mucus. May be light in colour and pasty.	Inoffensive
OTHER FLAGELLATE INFECTIONS	Gelatinous, mostly liquid faeces.	Offensive
BILHARZIASIS	Semi solid, chocolate coloured faeces thick blood and mucus, often in clumps, may be present or may be intermingled with the faeces.	Offensive
MUCOUS COLITIS	Stringy mucus intermingled with liquid or semi solid faeces. No blood, sometimes membrane.	Offensive
ULCERATIVE COLITIS	Thick blood and mucus with or without liquid faeces. Sometimes visible pus.	Very offensive, like stale blood.
POLYPOSIS	Dark coloured blood with small amount of mucus. No visible pus.	Offensive
POLYPUS	Whitish, thin mucus with or without faeces. Looks like sputum.	Inoffensive
INTESTINAL TUBERCULOSIS	Greenish brown liquid faeces containing intermingled blood and mucus.	Very offensive

Microscopically	Organism
Similar to sprue, but fatty globules present and fatty crystals usually arranged in spheres. Undigested food particles 'ciliated' Bacteria few	None incriminated
Similar to sprue, but fatty globules may be present Fatty crystals scattered Excess of starches Bacteria plentiful	None incriminated
No pus, mucous or blood cells Bacteria few Undigested food particles and fatty crystals, the latter arranged in bundles abundant, fatty globules usually absent Usually numerous <i>Blastocystis hominis</i>	Causal organism unknown
Red blood-corpuscles often in 'clumps' macrophage, pus, epithelial and shadow cells Bacteria few	Dysentery bacilli by cultural methods
Usually ordinary diarrhoeic picture, but sometimes few red blood and pus-cells	Typhoid and paratyphoid bacilli by cultural methods
Mucous and pus cells Blood-corpuscles absent Bacteria scanty	Cholera vibrio by cultural methods
Red blood-corpuscles very few pus-cells, mucous and epithelial cells Charcot Leyden crystals, free forms of <i>E. histolytica</i> , active, containing R B C's Bacteria numerous	<i>Entamoeba histolytica</i> Confirmed by appropriate staining methods
Red blood-corpuscles pus, mucous and epithelial cells present Charcot Leyden crystals absent <i>Balantidium coli</i> present Bacteria abundant	<i>Balantidium coli</i> Confirmed by appropriate staining methods
Numerous mucous cells, occasionally pus-cells R B C's rare Active <i>Giardia (Lambia) intestinalis</i> free if mostly mucous Numerous cysts if mucus scanty Bacteria few	<i>Giardia (Lambia) intestinalis</i> Confirmed by appropriate staining methods
Few mucous cells, no pus-cells <i>Trichomonas hominis</i> or <i>Chilomastix mesnili</i> free forms present Bacteria abundant	<i>Trichomonas hominis</i> <i>Chilomastix mesnili</i> etc
Similar to amoebic dysentery Charcot Leyden crystals often present, typical ova of <i>B. mansonii</i> or <i>B. japonica</i> present, but usually scanty, rarely, <i>B. hamatobia</i>	<i>Bilharzia mansonii</i> <i>B. hamatobia</i> , or <i>B. japonica</i>
Mucous and epithelial cells abundant, arranged in strings No red blood-corpuscles Undigested food remains abundant Bacteria numerous	No definite organism responsible
Similar to amoebic dysentery, but large numbers of pus and macrophage cells Charcot Leyden crystals often present Bacteria scanty	No definite organism responsible
Large numbers of red blood corpuscles in clumps Columnar epithelial cells and few pus-cells Bacteria scanty	None incriminated
Mostly mucous cells Few pus-cells Bacteria scanty	None incriminated
Red blood-cells, pus, mucous and epithelial cells present Bacteria few	Tubercle bacillus confirmed by appropriate staining

TABLE XIX.—BIOLOGICAL REACTIONS OF PATHOGENIC AND ALLIED ORGANISMS RECOVERED FROM THE FLEETS

	Mannite		Glucose		Maltose		Lactose		Saccharose		Ducate		Litmus or Phenol Red Milk			Indole	Mouldy
	A	G	A	G	A	G	A	G	A	G	A	G	A	Alt	Clot		
<i>Bact. shige</i>	0	0	+	0	0	0	0	0	0	0	0	0	+	0	0	0	0
<i>Bact. flexneri</i>	+	0	+	0	+	0	0	0	0	0	0	0	+	+	0	0	0
<i>Schmitz's bacillus</i>	0	0	+	0	0	0	0	0	0	0	0	0	+	0	0	+	0
<i>Sonne's bacillus</i>	+	0	+	0	0	0	+	0	+	0	0	0	+	0	+	0	0
<i>Bact. dispar</i>	+	0	+	0	0	0	+	0	0	0	+	0	+	0	+	+	0
<i>Bact. morganii</i>	0	0	+	+	0	0	0	0	0	0	0	0	0	+	0	+	+
<i>Bact. typhosum</i>	+	0	+	0	+	0	0	0	0	0	0	0	+	0	0	0	+
<i>Bact. paratyphosum</i> 4	+	+	+	+	+	+	0	0	0	0	+	+	+	0	0	0	+
* { <i>Bact. paratyphosum</i> B <i>Bact. enteritidis</i> }	+	+	+	+	+	+	0	0	0	0	+	+	+	+	0	0	+
	+	+	+	+	+	+	0	0	0	0	+	+	+	+	+	0	+
<i>Bact. coli</i>	+	+	+	+	+	+	+	+	0	0	+	+	+	+	0	+	+
<i>Bact. faecalis alkaligenes</i>	0	0	0	0	0	0	0	0	0	0	0	0	+	0	+	0	+
<i>Bact. acid lactici</i> (Häppler)	+	+	+	+	+	+	+	+	0	0	0	0	+	0	+	+	0

\* To differentiate *Bact. enteritidis* and other organisms of the food poisoning group from *Bact. paratyphosum* B serological tests must be applied

clear or granular, movement sluggish or active, position of the karyosome, presence or absence of included red blood corpuscles. It is unusual to find free amœbæ, other than *E. histolytica* or *E. coli* in a blood and mucus stool, and to find the latter in inflammatory exudate is such a rare event that, if the morphological differences between these two types are clearly understood, (see p 533), mistakes should not occur. Unfortunately, *Entamoeba histolytica* cannot always be found in a stool from a case showing all the clinical signs of amœbic dysentery. There is an instance of such a stool being examined by forty six students in a Tropical Medicine course, and in only one preparation were typical *E. histolytica* seen, a 24 hour culture on Boeck and Drbohlav's medium made from the same stool at the same time showed, however, numerous amœbæ. The explanation may lie in the fact that amœbæ are often discharged from the bowel into the faecal contents in "pockets," and by chance one of these "pockets" was inoculated into the culture medium and another selected by the student. If such a "pocket" is fortunately picked up the microscopic picture is remarkable—dozens of typical amœbæ may be seen in the field. It follows, therefore, that in the examination of a stool from a suspected amœbic dysentery case, one negative slide is not sufficient, and several portions from various parts of the stool should be searched. If the stool remains negative on one microscopical examination, further specimens should be searched. It is a well-established fact that amœbæ may be entirely absent on one day, and on the following be extraordinarily abundant. This applies equally to cysts.

If the stool consists of liquid faeces, a drop of normal saline or 1 per cent watery eosin is placed at one end of a slide and a drop of Weigert's iodine at the other. A portion of the faeces is first rubbed into the saline or eosin solution drop with the aid of a match stick, and then a portion is emulsified in iodine, and the resultant mixtures, which should not be too thick, are covered with cover glasses. The saline or eosin portion of the slide is examined under the  $\frac{1}{2}$  in objective for amœbæ, flagellates, or cysts. After a little experience, the eye is arrested by the opaque or ground glass appearance of protozoa. It is often possible to distinguish nuclei and chromidia in the saline specimen, perhaps more easily if eosin is added, but it is generally necessary to search an iodine preparation to recognize the finer points. Of the flagellates no difficulty is experienced in recognizing the characteristic free forms of *Giardia (Lamblia) intestinalis* (or its cysts), but with *Chilomastix mesnili*, *Trichomonas hominis*, and others, it is advisable to leave the slide for half an hour or longer until rapid movement has ceased, when the structure becomes more easily discernible.

In the examination of a suspected amœbic dysentery stool, care should be taken not to mistake the macrophage cells found in bacillary dysentery and in ulcerative colitis for *Entamoeba histolytica* (Fig 101). It is advisable for the beginner never to make a diagnosis of amœbic dysentery unless typical *E. histolytica* individuals are seen, showing the characteristic amœboid movement and containing enclosed red blood cells. It must be borne in mind that often only a few of the amœbæ contain ingested red blood cells. Similarly not every *E. histolytica* cyst shows the characteristic four nuclei and chromidia. Where any doubt exists, staining should be resorted to, for free amœbæ the rapid phosphotungstic acid hæmatoxylin is recommended, and for cysts the iron hæmatoxylin method (see p 575).

*Concentration methods for E. histolytica cysts*—C. F. Craig ('Amœbiasis and Amœbic Dysentery') recommends the emulsification of a portion of faeces

about the size of a pea in 10 c c of normal saline in a test tube. This mixture is strained through a double layer of cheese cloth and is then transferred to a centrifuge tube, which is filled to the top with saline and is centrifugalized at a moderate speed for 3-4 minutes. The sediment is then examined for cysts directly or with the addition of Weigert's iodine.

Yorke and Adams emulsify a walnut sized portion of the suspected stool in tapwater. The mixture is made up to 500 c c, placed in a tall glass cylinder, and stood aside for half an hour. It will then be found that a scum has formed at the top of the fluid, and a considerable amount of sediment has fallen to the

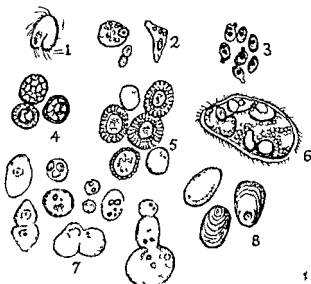


Fig. 101.—Objects in feces likely to be mistaken for amœbæ or cysts

- 1 Trypsin acids (peculiar form). 2 Mucous cells. 3 Yeast cells. 4 Spores of fungus.  
5 Cells from peas. 6 Streptococcus cell of bean. 7 Macrophages and other leucocytes.  
8 Starch granules.

bottom, while the bulk consists of fecal suspension containing the cysts. The scum is carefully removed with blotting paper. The suspension is poured into a clean cylinder, leaving the sediment behind and is allowed to stand over night. The cysts will by then have fallen to the bottom. The supernatant fluid is syphoned off and the deposit is transferred to centrifuge tubes. This is washed several times by shaking up with tapwater and centrifugalizing. Finally the deposit is transferred to a slide, mixed with iodine solution and examined under the  $\frac{1}{4}$  in objective.

#### BACTERIOLOGICAL EXAMINATION OF FECES

**For dysentery bacilli.**—If the stool is composed of blood and mucus only, a loopful is 'sown' into a tube of salt solution as soon as possible after passage, and is thoroughly shaken up. Plates of McConkey or Conradi-Dragalski medium are poured and when the medium has set, are turned



upside down with the top portion of the plate overhanging the bottom so to allow a current of air to pass. They are then put out to dry. Without disturbing the sediment, a platinum loopful of the emulsion in the tube is placed on the surface of the medium. With an L shaped sterile glass rod the drop of suspension is rubbed well into the surface of the medium. A second or third plate may be similarly treated with two or three loopfuls of the emulsion, but usually one is sufficient.

If the stool contains faeces, as well as the blood and mucus a portion of the latter is removed, washed in sterile normal saline and transferred to a second tube of saline or peptone water. It is well shaken and treated as above. When the dysenteric process subsides and blood and mucus are absent it is usually difficult to isolate the causal organism but sometimes a positive result may be obtained if the stool is freshly passed. In this instance a loopful of the diarrhoeic stool is transferred to the saline or peptone water tube and is treated as above. It is essential to bear in mind that even in the acute stages dysentery bacilli exist in small numbers in the exudate and that there are comparatively few other intestinal organisms. M. Haynes (1942) has found the rectal swab method of obtaining material for culture for dysentery typhoid organisms superior to the direct stool culture method. Unless the swab can be cultured very soon after taking it should be kept moist by immersion in saline agar. Swabs thus preserved from patients with typhoid, paratyphoid and Sonne dysentery have still yielded a positive culture after four days storage at room temperature in the dark.

The beginner must be warned that a preliminary incubation in broth or other medium with a view to enriching the subsequent culture is contra indicated.

After spreading the plate is incubated at 37° C. for eighteen hours by which time Shiga or Flexner colonies become apparent as clear bluish grey droplets with a regular or slightly wavy margin while Sonne colonies are irregular, the centres having a faint pink tinge where delayed fermentation of lactose is commencing. Sonne's bacillus tends toward symbiosis i.e. colonies are often found merged into those of other organisms. A better idea of the translucency of dysentery colonies may be obtained by examining by reflected light against a dark background with the aid of a hand lens. Dysentery colonies are usually the smallest non lactose fermenters on the plate and they occur in irregular chains interspersed between the large pink colonies of *B. coli* and other organisms. In order to accentuate the characteristics of dysentery colonies it has been found helpful to place the plate in an ice chest for three or four hours.

*Method of recognizing the bacillus* —In order that bacteriological diagnosis shall be the efficient handmaiden of clinical medicine it is necessary that methods should be evolved which will give a positive diagnosis within a reasonable and practicable time. The likely colonies should be picked off sown on separate broth tubes and incubated for twelve hours. The growth which is scanty and tends towards opalescence (a heavy growth means that the organism is definitely not the dysentery bacillus) should then be examined microscopically, and subsequently tested out by means of biochemical and agglutination tests.

*Macroscopic agglutination tests* —In order to perform this test an emulsion is made of the organism in 0.2 per cent. formal saline solution which should become distinctly opalescent. It should then be dropped by means of a small bore pipette into narrow glass agglutination tubes containing an equal

quantity of immune rabbit serum in various dilutions for agglutination to occur

Carrow's agglutinator is an instrument by which it is possible to recognize suspicious dysentery colonies on a plate by means of macroscopic agglutination. Emulsions are made of the colonies in small quantities of formal saline and are then placed upon a glass slab and intimately mixed with an equal drop of a diluted Shiga, Flexner or Sonne serum in a dilution of 1:100.

*Considerations on which successful isolation of the dysentery bacillus depends*—1 Period of the disease. It is an accepted fact that dysentery bacilli are most numerous in the exudate in the early stages of the disease, but after the sixth day their isolation becomes a matter of increasing difficulty.

2 It is not possible to isolate the dysentery bacillus from every suitable stool at the first attempt. This is especially the case with the stool of the very acute or fulminating forms of the disease which is passed early in such an attack and contains much dark and altered blood. The author has frequently succeeded in isolating the bacillus on the second and third attempt.

3 Failure to isolate the bacillus from the stools does not necessarily indicate that it is not present in the intestinal canal of the patient. It is quite obvious that this is comparatively frequent. It has been proved that the bacillus can be recovered at autopsy from the bases of chronic ulcers in the intestine in cases where a search during life has been vain.

4 The character of the cellular exudate may be taken as an index of the probability of successful culture. Those stools which contain the largest number of undamaged pus cells and red blood corpuscles and the fewest contaminating bacilli are the most favourable.

5 Under tropical conditions the isolation of the dysentery bacillus can be made with great difficulty after the stools have been passed for four hours. It has been shown that stale specimens of stool become readily overgrown with *B. coli* and other saprophytic organisms.

6 The nature of the contaminating organisms. Difficulty in isolating the dysentery bacillus may be ascribed to the presence of bacteriophage in the exudate, and it is certain that it may also be due to the presence of *B. pyocyaneus* which is a frequent concomitant. The difficulty of successful isolation is increased should any quantity of urine be present.

The following table is compiled from the records of 250 cultures of bacillary dysentery stools which were undertaken in Palestine in 1917. It serves to indicate the probability of successful isolation of dysentery bacilli at the first attempt.

Character of specimen	Successful isolations
Fresh gelatinous, blood-stained mucus. Cellular exudate—fresh pus-cells, red cells and few visible bacilli.	73.3 per cent
Glaucous mucus. No blood. Cellular exudate—pus-cells and macrophages.	67.5 "
Blood and mucus. Disintegrating pus-cells and numerous motile bacilli.	41.8 "
Bile-stained blood and mucus. Disintegrating bile-stained pus-cells and red cells.	33.0
Blood and mucus flakes intermingled with feces.	31.7

*Isolation of bacilli from carriers*—This procedure should be carried out in the same manner as for carriers of the typhoid group. In order to test speci-

mens satisfactorily, at least five platings are necessary and the faeces should be collected on a sterile swab. The minute portions of faeces so removed should then be thoroughly emulsified in 5 c. c. of sterile saline and spread in a spiral manner on a suitable plate, using progressively smaller quantities of the emulsion for each successive plate.

*Isolation of the dysentery bacillus post mortem*—The bacillus can be isolated with comparative ease from the early lesions of bacillary dysentery in the large intestine by washing the mucous membrane free from intestinal contents and then making a scraping with a platinum loop, and plating out.

From necrotic tissue, isolation is by no means so easy, as the membrane is usually swarming with organisms which rapidly overgrow the plate and so inhibit the growth of the dysentery bacillus. In these cases it is necessary to flush out the bowel, dry with a sterile swab, scar the exposed surface with a hot rod and then incise it with a sterile knife. A platinum loop is then plunged into the incision and some fluid is expressed and spread as evenly as possible upon McConkey, or desoxycholate citrate agar.

The isolation of the organism from chronic ulcers is a matter of still greater difficulty. The ulcers must be freed from sloughs, cleansed, and scraped before the bacillus can be obtained. According to the author's experience, Shiga's bacillus is nearly always responsible for the most acute and rapidly fatal forms of the disease.

It has been recorded that dysentery bacilli may be isolated from the mesenteric glands and occasionally from the blood stream but this is by no means common.

*Viability of the dysentery bacillus*—Fletcher and Jepps have made direct experiments to ascertain the viability of the dysentery bacillus, and they found that Shiga bacilli disappeared within twenty four hours from ten out of fifteen samples of acute dysenteric faeces kept at room temperature, but that Flexner bacilli were capable of surviving for considerably longer periods, in over half the specimens they persisted for more than one week. Presence of faecal matter and the resulting acidity generally destroy dysentery bacilli. By mixing with glycerin the organisms survived much longer in an alkaline medium, but there was a drop in the number of bacilli at the end of thirty six hours. A practical experiment in the collection of dysenteric faeces in the field showed the value of this method. Martin and Williams, from their experiences in the Mediterranean and in Egypt in 1915 and 1916, concluded that the chance of recovering dysentery bacilli from the stools after the first few days progressively diminished, a host of intestinal organisms appearing to overwhelm those dysentery bacilli originally present. Out of 1,050 efforts to recover dysentery bacilli from the stools, 68 per cent. positive results were obtained in the first five days, 17.4 per cent. on the sixth to tenth days, and 6.3 per cent. on the eleventh to thirteenth days.

L. Dodgson (1918) has made the important observation that the addition of alkali to dysenteric or diarrhoeic stools permits the cultivation of dysentery bacilli while acid has a directly opposite effect. This beneficial action can be utilized by adding and intimately mixing 3 per cent. normal sodium hydrate with each sample immediately it is collected.

Twenty-one fresh samples of blood and mucus mixed with faeces were found to be alkaline to litmus, while dysentery bacilli were cultivated from fourteen of these specimens ten hours later, in the majority of the negative specimens the reaction was acid. The addition of the necessary quantity of alkali resulted in no less than twenty of the specimens remaining alkaline during the entire course of the experiment, while dysentery bacilli were cultivated on ten occasions.

## ISOLATION OF THE DYSENTERY BACILLUS FROM HOUSE FLIES

The following technique for the isolation of the dysentery bacillus from house flies was adopted by the author in Fiji. Four to six flies were caught on dysentery patients or in the dysentery ward. They were chloroformed and dropped into a tube of sterile saline. After removal they were dissected with the aid of sterilized Hagedorn needles on sterile slides, the abdominal segments being separated and the intestines drawn out. A small portion of intestine was divided by means of a sterile platinum loop and emulsified in broth or saline. Conrad Drigalski plates were then spread with the emulsion and incubated. On this medium Shiga's bacillus was isolated from the lower intestinal tract of the fly in two instances.

Feeding experiments were carried out with flies newly hatched from pupae which had been raised in as sterile a manner as possible. A watchglass containing sterile bread soaked in broth cultures of Shiga and Flexner bacilli was placed in sterilized cages each containing twenty house flies. In the majority of instances the organisms recovered from the flies gave the same biochemical and serological reactions as the bacilli which were originally used as the infecting agent, but variants which were morphologically similar to the type were recovered, such as Shiga bacilli which fermented maltose and Flexner bacilli which fermented maltose and saccharose.

In any further work undertaken upon the carriage of dysentery bacilli by house flies it must be borne in mind that, as pointed out originally by Graham Smith, many non-lactose fermenting bacilli found in the intestines of flies are indistinguishable culturally from *B. dysenteriae*.

## DESCRIPTION OF DYSENTERY BACILLI

Members of the dysentery group of bacilli are non-motile (rarely negative coiled bacilli indistinguishable morphologically from other members of the group *Bacterium*). Morphological and cultural variants have been described by several workers. As with other members of the *Bacterium* group, the antigenic structure is of far more importance in defining smooth and rough types than is the appearance of the colonies. The members of this group are not specially resistant; they are killed by a temperature of 55° C. for one hour or by 0.5 per cent. phenol in six hours and 1 per cent. phenol in fifteen to thirty minutes. They can resist drying for twenty to twenty-five days. Dysentery bacilli are aerobes and facultative anaerobes and the optimum temperature is 37° C. With the possible exception of *B. alkalescens*, none appear to be capable of producing an active haemolysin against sheep cells.

*B. shiga* and *B. schmitzi* produce acid from glucose, but the remaining members of the group ferment mannitol. *B. sonnei* and *B. dispar* produce acid from lactose. In litmus milk or phenol red milk there is generally a slight acidity which may remain permanent as with *B. sonnei* and *B. dispar* or it may revert to neutral after a few days as with *B. shiga*, *B. schmitzi* or *B. flexneri*; many strains of *flexneri* however after a preliminary acidity turn alkaline (Table XIX). *B. alkalescens* produces an initial lasting alkalinity.

Indole is of differential importance, distinguishing Schmitz's bacillus from *B. shiga* and *B. dispar* from *B. sonnei*. None give a positive Voges-Proskauer reaction. The serological behaviour of the dysentery bacilli is very complicated. For instance, the Shiga group is homogeneous—an anti-Shiga serum has some agglutinating action on some strains of the Flexner group.

Antigenically Schmitz's bacillus and Shiga's bacillus are easily distinguishable. Sonne's bacillus is antigenically homogeneous, while *B. dyspae* appears to be antigenically heterogeneous.

*Schmitz bacillus (Bacterium ambigua\*)*—This organism was first described in 1917 by Schmitz; it was accepted as a dysentery bacillus by Kruse who included it as Type J in his series. Murray (1918) found it among his collection of strains and it has since been recognized in many parts of the world. Evans (1938) attributed this organism to an outbreak of asylum dysentery in Wales and more recently it has been recovered from other asylum infections. It has been recovered post mortem from dysenteric lesions of the bowel and has caused a laboratory infection (Hirschbruch and Theim 1918). The organism is distinguished from Shiga's bacillus by the fact that it produces indole from peptone and serologically by the possession of a distinct antigen. In Boyd's experience the two organisms show no cross agglutination whatsoever.

*Flexner bacilli (Bacterium flexneri)*—The classification of Flexner bacilli has in the past presented several difficulties. This mannite fermenting group contains individuals which are by no means so well defined and stabilized as is the Shiga organism. The classification of Andrewes which was adopted at the end of the last war is a simplification of the problem, has recently been radically altered. A basis for sub-grouping was the serological method of Murray, Andrewes and Inman (1924). Five definite strains V W X Y Z were recognized and five homologous sera were prepared and for the general recognition of the Flexner group a pooled serum of the combined strains was generally employed, but now this basis of recognition has been considerably amplified and modified by J. S. K. Boyd (1940) who found considerable antigenic variation amongst the mannite fermenting group. He collected 7339 strains of dysentery bacilli from the military laboratories in India from 1932-35. Of these 14.3 per cent were Shiga, 5.5 per cent Schmitz, 10.9 Sonne, 50.2 per cent Flexner, 15.3 per cent definite lactose fermenters.

He recognizes Flexner types V W Z of Andrewes as valid and as possessing distinctive specific antigen, to these he adds a further three types. There are therefore six types—V W Z 103 'P 119 and 83 (the two latter identical with Newcastle and Manchester strains). In 103 strain the type specific antigen is lost. Under modern conditions pooled antigens of the six different types and pooled sera of the same are supplied for diagnostic purposes.

Agglutination of the dysentery bacilli occurs slowly. It is advisable to incubate the test tubes for two hours at 30° C.

No other member of the dysentery group is toxicogenic to anything like the same extent as is Shiga's bacillus.

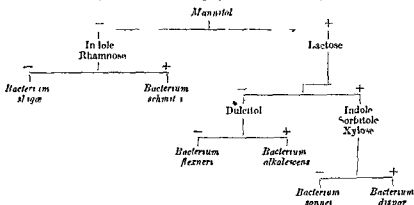
Most workers have completely failed to reproduce true dysenteric lesions in cats, dogs, rabbits or monkeys by injection either per os or per rectum with any members of the dysentery group.

*Sonne's bacillus (Bacterium dysenteriae sonnei)\**—Sonne's bacillus appears to have been found in the first instance by W. Kruse in 1900 and was termed by him and his collaborators (Ritterhaus, Kemp and Metz) who worked with him till 1907, the lactose fermenting or E. race of pseudo dysentery.

\* It has been pointed out on several occasions that strictly speaking the organism should be known as the Sonne-Dural bacillus.

TABLE XX

CLASSIFICATION OF BACTERIA OF THE DYSENTERY GROUP  
(After W W C Topley and G S Wilson)



bacillus. The term pseudo dysentery bacillus does not find favour in modern bacteriological circles. In 1904 the bacillus appears to have been rediscovered by Duval and then again a few years later, in 1912, by K. Baerthlein, who recovered it in a dysentery like epidemic in Berlin. In 1915 C. Sonne gave a detailed description of this organism during a similar epidemic in Copenhagen, and in 1917 Thjøtta in Norway showed that d'Herelle's new type of organism was identical with Sonne's bacillus. The organism has been found in England in 1923, by D. Nabarro, by A. M. Fraser, J. P. Kinloch, and J. M. Smith in Scotland, H. M. Perry in Egypt, E. Plockmann, W. E. Hilgers, and F. Sartorius in Germany, and by S. W. Patterson and F. E. Williams in Australia. A. de Assis and Mendes (1929) have isolated the organism in Rio de Janeiro and R. I. Nelson has found it widespread in children in Boston. In Japan it gives rise to acute dysentery in children known as "Chiri."

Originally the Flexner organism, Sonne's bacillus, and Schmitz's bacillus were included under the name *Bacillus pseudodysenteriae*. This classification is not used in England, as Flexner infections of great virulence have been reported and in 1933 it has been shown that the toxins of Sonne's bacillus can cause virulent symptoms simulating food poisoning. It is closely related to *B. dispar* (Table XX).

Sonne's bacillus is non motile, and in morphological characters resembles members of the Flexner group, colonies on gelatin and agar plates also resemble these organisms. W. R. Wiseman (1927) has pointed out the tendency of this organism to bipolar staining. It is capable of fermenting lactose jelly. On agar, two forms of colonies are found, one round and smooth, the other flat and irregular. On lactose litmus agar colonies are at first bluish, and later reddish, no indole is produced. Litmus milk remains unaltered at first, but lactic acid is produced and it gives a negative methyl red reaction. On McConkey's medium, Sonne colonies frequently show a small central point of acidity on an opaque background.

Care should be taken in examining these cultures, for while no isolated non lactose fermenting colony may be seen, colonies of *B. coli* with a slowly

spreading opaque edge will be found, from which Sonne can be isolated. This may be a case of symbiosis, or possibly of mutation, if the latter, it will be realized that different stages of mutation may occur, and it is thought that this may be one of the reasons for the varying accounts which have appeared of differences in sugar reactions, agglutinations, etc.

Primary cultures of Sonne's bacillus are not agglutinated by specific serum after four hours at 55° C but sub cultures later become agglutinable and all strains absorb agglutinins. Great variability in the serological properties of different strains have been reported. Sonne serum is more specific than that of Shiga and Flexner organisms. The serum of Shiga patients may agglutinate Flexner. Determination can finally be made by absorption. If the agglutinins are removed when saturated with Shiga serum, it means that the patient's serum contained Flexner co agglutinins. It has not been established that the serum of Flexner patients shows agglutinins for Shiga or Sonne.

Mutations do occur, and, as Sonne's bacilli vary in agglutinability, cultures should be planted on to agar and single smooth colonies taken to produce antigen for serum production or agglutination. Rough strains produce agglutinins in the serum of the rabbit, but the same serum may fail to agglutinate freshly isolated strains of Sonne especially if the cultures consist mostly of the smooth type. The production of agglutinating serum is not so easy in some strains as in others. Though not, generally speaking, as toxic as Shiga's bacillus, Sonne's bacillus when injected into rabbits may cause sudden death.

#### AGGLUTINATION OF DYSENTERY BACILLI WITH PATIENT'S SERUM

A simple method of macroscopic agglutination by progressive dilution of the serum in agglutination tubes can be employed, but it gives only a limited range of dilution and a considerable amount of blood (1-2 c c) is required. The glass capsules containing the blood should be centrifuged, and the serum abstracted by means of a pipette. At least five drops of clear serum are required in order to obtain a quantity sufficient for further dilution. This amount should be mixed with twenty drops of normal saline delivered from the same pipette held in a vertical position, in order to obtain a 1 : 5 dilution. For further dilution, twenty drops of the 1 : 5 dilution are placed in the first of a row of agglutination tubes after which ten drops are removed and mingled with an equal amount of saline in the second tube, thus giving a dilution of 1 : 10. From these twenty drops ten are removed and placed in a third tube, and so on, the dilution each time being doubled. To the ten drops of diluted serum remaining in each tube an equal amount of an opalescent emulsion of bacilli should be added, thus doubling the dilution of the suspension in which the organisms are placed. The tubes are incubated for two and a half hours or, preferably, for a shorter period at 55° C, and are then examined for agglutination against a dark background. This is generally sufficiently obvious when compared with control tubes in which bacillary emulsion diluted with saline or with normal serum has been placed. The objection to this method is the limited range of titre which it affords, in order to get a range of from 1 : 10 to 1 : 160, a row of five tubes is necessary.

In testing for dysentery agglutinins, three rows of five tubes each are necessary—one for Shiga, and one each for Flexner and Sonne.

In describing the various methods, the following abbreviations are commonly used, viz, "S" for Shiga, "F" for Flexner, "So" for Sonne.

A more accurate but more tedious method is Dreyer's drop method

for which standardized bacillary emulsions can be obtained. The standard culture is as sensitive to agglutination as is the fresh culture, it is, moreover, sterile and, if stored in a cool dark place, can be kept indefinitely.

The highest dilution in which marked agglutination, without sedimentation occurs and can be detected by the naked eye, is termed *standard agglutination*. When this occurs with *standard agglutinable cultures* in a serum diluted to a certain degree, then the latter figure, divided by the number given on the label of the culture employed, gives the number of *standard agglutination units* contained in 1 c.c. of the serum examined.

A stand containing fifteen small agglutination tubes in three rows of five each and two larger dilution tubes should be taken. With a dropping pipette measure out into one large dilution tube fifty four drops of normal saline solution (0.85 per cent sodium chloride in distilled water) by means of gentle pressure on the teat. Wash the pipette with distilled water, and subsequently with absolute alcohol and ether, so as to dry thoroughly. Take up the serum to be tested into the dried pipette. Measure out six drops of the serum into the dilution tube already containing the fifty four drops of saline, thus obtaining a dilution of 1 : 10.

The second tube should be taken, and three drops of the 1 : 10 serum dilution added to fifty seven drops of normal saline, this gives a dilution of 1 : 200. The pipette should be carefully washed out and to each tube in the row fifteen drops of standard agglutinable emulsions of S, F, and So added. Thus —

①	②	③	④	⑤	①	②	③	④	⑤	①	②	③	④	⑤
S					F					So				
15 drops					15 drops					15 drops				

For the addition of the diluted serum it is best to commence with higher dilutions before proceeding to the lower ones. To tube 3 in each row add ten drops of 1 : 200 serum, to tube 4 in each row add five drops of 1 : 200, to tube 1 add ten drops of 1 : 10 dilution, and to tube 2 also add two drops of 1 : 10 dilution. The pipettes must be washed out before proceeding to add the saline. The addition of saline should then be made to tubes 2 and 4, which receive eight and five drops respectively, while tube 5 receives no serum, but ten drops of saline only, and acts as a control against spontaneous agglutination. This can be best represented by the following scheme —

No. of tube	Drops of normal saline	Drops of serum	
		Dilution of	1 : 200
1	0	10	
2	8	2	
3	0	10	
4	5	5	
5	10	0	



It will be noted that the final volume of fluid in each tube, when the bacillary emulsions are added, is twenty five drops. By calculation it will be seen that in tube 1 of each row the serum acts in a dilution of 1 : 25

In tube	2	in a dilution of	1	125
"	3	"	1	500
"	4	"	1	1 000

The tubes are examined after four hours at 37° C., or two hours at 50°–55° C., followed by fifteen minutes at room temperature. The reading is taken by comparing each tube in succession with the control tube, and is

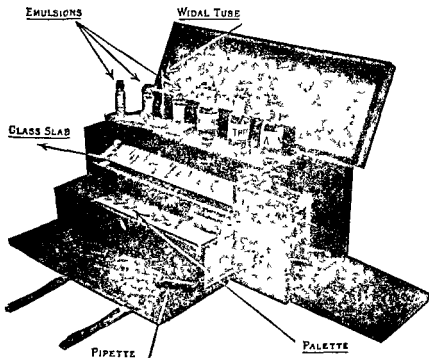


Fig 102 —Garrow's agglutinator, showing instrument ready for use \*

preferably made by means of artificial light against a black background. If daylight is used, the tubes should be partly shadowed by passing a finger up and down behind them.

**Rapid method of macroscopic agglutination by Garrow's agglutinator (Fig 102).**—This is a practical method suitable for small laboratories and is based upon the slide method of agglutination originally described by Broughton Alcock. It may be used for recognition of pathogenic bacteria isolated from the blood or excreta by means of specially prepared serums. Macroscopic agglutination becomes visible in as short a period as three minutes, no incubator is needed.

\* This instrument can be obtained from Messrs Baird and Tatlock Ltd, Cross Street, Hatton Garden, London, E C 1.

For use the following apparatus is required —

(1) A *painter's palette* (Fig. 103) for dilution of the serum (2) A *diluting pipette* drawn from glass tubing  $\frac{1}{8}$  in in diameter and 6 in in length. The latter should deliver a drop of satisfactory dimensions (a Donald's pipette

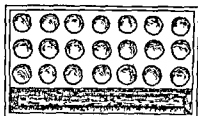


Fig. 103 — "Palette" for diluting serum, used with the agglutinator

fitting Morse gauge No. 70 is the correct size)—that is, when mingled with an equal quantity of bacterial emulsion, it should not run over the edge of the glass slab (Fig. 104). (3) The *agglutinator slab*, a piece of plate glass  $11\frac{1}{2}$  in long by  $1\frac{1}{2}$  in wide, divided into a number of partitions by double grooves running at regular intervals of 1 cm in order to prevent the dilutions from intermingling (Fig. 106). (4) *Set of bacterial emulsions*. The stock emulsions for use with the agglutinator for diagnosis of the dysentery group are *B. shigae*, *B. flexneri* and *B. sonnei*. They are made from 24 hour surface agar cultures. The growth is scraped (not washed) off the surface by means of a platinum loop and emulsified in 0.2 per cent formalin in normal



Fig. 104 — Drop pipette used with the agglutinator

saline. The emulsions should be very dense of milky consistence and uniform suspension.

In order to promote the intimate mixture of the serum under investigation and the bacterial emulsions the slab is made to revolve by clock work at a uniform rate of about fifteen revolutions per minute. For field use the slab may be placed in a simple box provided with damp blotting paper in order to obviate desiccation, and turned by hand with a handle attached to a wooden shaft which supports the glass slab.

*The diluting process*—The blood for examination is taken from the finger and collected in a capillary. Three large drops of blood are sufficient, the ends of the tube are sealed with wax or plasticine (Fig. 105). After stand-



Fig. 105 — Special straight capillary tube for collecting serum.

ing for some time the serum separates rendering centrifugalization unnecessary. By means of the pipette two drops of clear serum are abstracted and placed in the first partition of the mixing palette. In order to make a dilution of 1:5, eight similar drops of normal saline are added. From the

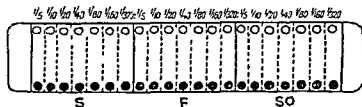
resulting ten drops of diluted serum, five are then placed in the next partition and a similar amount of saline added, and so on, thus making a series of dilutions from 1/5 to 1/80 or higher. It is important that the pipette be held vertically throughout the process, to ensure equality in size of the drops.

*The mixing process* —The process of mixing the blood serum and bacterial emulsion is carried out on the agglutinator slab. It is essential that the slab be perfectly free from grease, or the drops will not run together. It should be cleaned after each test by (1) washing in 1/20 carbolic acid, (2) cleansing with alcohol, and (3) drying with ether. It is a good plan to keep a piece of old linen specially for this purpose. In cold weather the drops can be made to run more freely by gently heating the slab before use or by breathing on it before the drops of bacillary emulsion and serum dilutions intermingle.

Holding the pipette vertically, begin with the highest dilution and deposit drops of the various dilutions of serum in triplicate on the slide. Opposite each drop of serum place a drop of bacterial emulsion, sterilizing the pipette by drawing into and expressing from it (1) alcohol, (2) ether, between each emulsion.

Fig 106 shows the appearance of the slab after carrying out the above process.

*Dilutions of serum*



The slide so prepared is placed in the moist chamber of the mechanical mixer, where it is held fast by means of a clip at each end of the shaft. The clockwork is put into operation and the slide is allowed to revolve slowly for three minutes. The result is that the drops of diluted serum run into and mix freely with the corresponding drops of bacterial emulsion, producing mixtures having serum titres of 1/10, 1/20, 1/40, and so on (Fig. 107).

At each complete revolution of the slide the bulk of these mixtures runs to and fro across the slide. At the end of three minutes the clockwork is stopped and the slide removed, and examined by the naked eye (if necessary, by a pocket lens) in a good light against a dark background. Agglutination converts the mixtures from homogeneous milky emulsions into a condition in which the agglutinated masses of bacilli float about like minute flakes in a clear fluid. In a strongly agglutinating serum this takes place almost instantaneously after the agglutinator slab begins to revolve. In higher dilutions the change may take three to four minutes, and be observable only with the aid of a pocket lens. If no change is visible with the pocket lens in the 1/10 dilution at the end of five minutes no agglutination of any diagnostic significance is present in the blood.

Fig. 108 shows the appearance of the agglutinator slide in the case of a patient whose blood agglutinates S up to 1/320, SO up to 1/100, the Flexner emulsion being negative.

#### AGGLUTINATION TESTS

An emulsion of a pure culture of the organism is made in saline and tested on the agglutinator or in tubes, against specific serums. In routine examinations it is convenient to keep the stock dilution of the serum (say 1/50) in small rubber stoppered bottles in 0.5 per cent. carbol saline. If the organism is agglutinated in a dilution of 1/100, it is tested against higher dilutions and the titre thus determined.

The effects of heat on the various agents concerned in agglutination has revealed marked differences in the heat stability of different bacterial antigens and of the reacting agglutinins. There are heat labile antigens which cease to react with the corresponding agglutinins after being heated for one hour at temperatures varying between 62° and 75° C. The second group of antigens is heat stable.

In many cases, differences in the character of the clumps formed during flocculation are noted. The interaction of heat labile agglutinogens and the corresponding agglutinins leads to the formation of loosely knit clumps, like flakes of snow, which form a bulky precipitate but which are readily broken up on shaking. On the other hand the interaction of heat stable agglutinogens with the corresponding agglutinins leads to the formation of smaller but tighter clumps which settle as a granular deposit and which are not easily redispersed by shaking. The heat-labile antigens and their antibodies are known as "H," while the symbol 'O' is used for the heat stable antigens. Any agglutinin which is produced in response to the inoculation of a particular antigen must be regarded as homologous with it. Heterologous strains can be distinguished by serological methods which demonstrate differences in their antigenic components. It is therefore possible to estimate quantitatively the antigenic content of a given serum and further to distinguish agglutinins due to inoculation from those produced as a result of direct infection with living bacteria. The heat labile "H" agglutinins are associated with the flagella of the bacteria, while the heat-stable "O" agglutinins are contained in the bacillary bodies.

**Isolation of the cholera vibrio from fæces.**—For the isolation of the cholera vibrio, a loopful of the suspected stool is inoculated into peptone water which is then incubated at 37° C. The organism grows rapidly, is strictly aerobic, is motile, and may be demonstrated by taking a loopful of the fluid from the surface of the peptone culture in from three to eight hours of 'sowing'. Should a pellicle have formed at the surface of the medium, the tube is slightly tilted and a loopful of the culture is withdrawn without disturbing it. A hanging drop preparation is tested for motility, while an ordinary smear, after drying, is stained with one of the aniline dyes and is examined for the presence of the typical vibrios. Plates containing one of the selective media, and previously dried off, are now sown from the surface of the peptone culture, and are incubated overnight at 37° C. The peptone culture is returned to the incubator and in twelve to twenty four hours is tested for the cholera red reaction. This consists of adding three to five drops of concentrated pure sulphuric acid to the culture when if positive, a rose red colour develops. Some brands of peptone inhibit the reaction, and in some instances the reaction is positive only when there is a pure culture of the vibrio. After incubation the plates are examined for typical colonies of the organism and agglutination tests are performed.

The colonies emulsify with great ease. A simple and rapid method is to make two vaseline circles side by side on a microscopic slide. Inside one ring is placed a loopful of normal saline and in the other a loopful of 1:1000 cholera serum, to each is now added a loopful of a saline emulsion of one of the suspected colonies. The circles are covered with cover glasses and examination is made under the low power of the microscope. The diluted serum preparation if positive, quickly shows absence of motility and curdy agglutination, while the other remains uniformly turbid and shows motility.

**Isolation of the tubercle bacillus from fæces.**—Baldwin Petroff and Gardner recommend the following method. Morning specimens of stool are collected in wide mouthed bottles and diluted with two volumes of distilled water. The mixture is stirred and filtered through gauze to remove coarse particles. The liquid is then saturated with sodium chloride and allowed to stand at room temperature for several hours. At the end of this time the bacteria will have floated to the surface and the scum can be collected with a sterile spoon and transferred to a clean wide mouthed bottle. Two volumes of normal caustic soda are added and the mixture is well shaken and incubated for one to two hours at 37° C. The specimen is now centrifuged, the clear fluid decanted, and three or four drops of normal HCl are added to the deposit. The sediment may be divided into three portions, one for staining, one for inoculation into suitable media and the third for animal inoculation. It must be borne in mind that not all acid fast bacilli found in fæces are tubercle bacilli, it has been repeatedly demonstrated that non pathogenic acid fast organisms may be present.

**Pappenheim's stain for tubercle bacilli.**—This method is employed to safeguard against confusing *B. smegma* and other acid fast bacteria with the tubercle bacillus. After customary staining with carbol fuchsin the decolorizing is carried out with 1 per cent rosolic acid in absolute alcohol saturated with methylene blue and 20 per cent glycerol. It is claimed that only true tubercle bacilli retain the carbol fuchsin stain after this treatment.

## CULTURE MEDIA FOR INTESTINAL PROTOZOA

## 1. For the cultivation of amœbæ.

*Boeck and Drbohlav's medium (L E S)*—Four hens' eggs are washed in water, wiped with alcohol and broken into a sterile, wide mouthed, stoppered bottle containing glass beads. Fifty c c of Locke's solution are added and the bottle is well shaken to effect solution. Test tubes are filled with a sufficient quantity to produce slopes one and a half inches long, slanted in an inspissator and heated to 60° C for one hour. On the second day the tubes are again inspissated at 60° C for one hour, and on the third the temperature is raised to 80° C for one hour. To each tube is now added eight parts of Locke's solution and one part of inactivated human blood serum till the liquid reaches the top of the solid egg column. Both the Locke's solution and the human serum must be sterile. If the sterility of the serum is doubted, it should be diluted with two or three parts of Locke's solution and filtered through a Berkefeld filter (No. N) once or twice to remove contaminating bacteria. When sterile it is further diluted with Locke's solution to bring the dilution to 1 : 8.

## LOCKE'S SOLUTION

Sodium chloride	5.0	gm
Calcium chloride	0.24	gm
Potassium chloride	0.12	gm
Sodium bicarbonate	0.2	gm
Glucose	2.5	gm
Distilled water	1 000	c c

The best growth of amœbæ occurs when the reaction of the medium is between pH 7.2 and 7.8.

*Boeck and Drbohlav's medium (L E A)*—A modification of Boeck and Drbohlav's medium (L E S) is L E A which has the advantage of being more readily prepared. Albumin solution instead of serum is added to the egg slants. This albumin solution is prepared by adding well whipped white of one egg to 1 000 c c Locke's solution. The mixture is then filtered through a Berkefeld filter candle (No. N) with a suction pump. It will be found necessary to wipe the candle with sterile cotton wool periodically as it becomes clogged. Ordinary blood agar slants may be used in place of the egg slants.

*Dobell and Laidlaw's medium*—Dobell and Laidlaw find that the richest and most prolonged growth of amœbæ is obtained on a medium having coagulated horse serum as the solid constituent and Ringer's solution as the liquid together with powdered rice starch. To prepare the medium, suitable volumes of horse serum sterilized by filtration are placed in tubes with aseptic precautions and inspissated at 80° C for one hour. It is important not to over heat the serum. Ringer's solution, containing the whipped whites of four eggs per litre and previously sterilized by filtration through a candle filter is now added to the top of the column in each tube.

## RINGER'S SOLUTION

Sodium chloride	9.0	gm
Potassium chloride	0.2	gm
Calcium chloride	0.2	gm
Distilled water	1 000	c c

Before inoculation, powdered rice starch is introduced into the medium, which falls to the base of the tube. The starch should be dry, and packed in small test tubes, and sterilized in a hot oven at a temperature of 180° C.

Cultures are made on any of these media by introducing into it a small

quantity of infected mucus or faeces. The material is inoculated into the bottom of the tube with the aid of a wide bore pipette, and the tubes are incubated at 37° C. Cultures may be examined twenty four hours later, when material is removed from the bottom of the tube by means of a pipette. It is advisable to scrape the surface of the egg or serum slope with the pipette to remove adherent amœbæ before sucking up a sample. Sub cultures should be made every four to six days. When rice starch has been added, it will be found that amœbæ have ingested the smaller particles. Cysts may be produced.

## 2. For the cultivation of intestinal flagellates.

*Tanabe's medium* — This is prepared by mixing —

Sodium chloride	0.7	gram
Sodium citrate	1.0	gram
Distilled water	100	c c

Sterilize in the autoclave or by boiling, and when cool add 0.5 gramme of Loeffler's dehydrated blood serum and 2 c c of whipped white of a hen's egg prepared as aseptically as possible. Fill into test tubes about 10 c c to each and warm to 37° C before inoculating with infected faeces.

By using an agar slope in conjunction with this medium, growth of the flagellates tends to concentrate to the bottom of the tube. The agar is prepared as follows —

Agar	15	gram
Sodium chloride	1	gram
Distilled water	900	c c

Steam this for one hour to dissolve the agar, filter through cotton wool fill into test tubes, 5 c c in each, sterilize in the autoclave and allow to cool in a sloping position. Store in a cool place. Before using, heat the liquid medium to 37° C and add to the top of the agar slope. The cultures are examined by removing some of the material from the bottom of the agar column with the aid of a long wide bore pipette.

Most of the intestinal flagellates (but not *Giardia (Lamblia) intestinalis*) have been cultivated on this medium. It has also been used successfully for cultivation of *Balantidium coli*.

## SELECTIVE MEDIA FOR THE ISOLATION OF ORGANISMS OF THE DYSENTERY-TYPHOID GROUP

*McConkey's bile salt lactose agar* — To 1 000 c c of distilled water in a flask is added —

Agar powder	25	gram
Leptone	20	gram
Sodium taurocolate	5	gram

Mix thoroughly and steam at 100° C for two hours. Cool to about 60° C and adjust reaction to pH 7.8-8.0. Add the well whipped whites of two eggs and return to the steamer to clear. Filter through thick Chardine filter paper. Add 10 grammes of lactose and 2.5 c c of a 1 per cent watery solution of neutral red. Tube off, about 10 c c to each tube, and sterilize for thirty minutes at 100° C on three successive days.

On this medium *B. coli* colonies are bright pink, streptococcal colonies small and deep red, and colonies of *B. dysenteriae* and *B. typhosus* bluish grey "dew drop".

*Conradi Drigalski medium*—To 1,000 c c of distilled water in a flask is added—

Leptone	10	gm
Nutrose	10	gm
Sodium chloride	5	gm
Meat extract (Lemco)	5	gm

Mix thoroughly and steam for one hour at 100° C

Now add agar powder, 25 grammes Steam for a further two hours When cool, add the whipped whites of two eggs heat again till clear, and filter through thick Chardine filter paper

Boil 65 c c of litmus solution (litmus crystals covered with distilled water boiled for half an hour filtered, and made up to the original volume with distilled water) and add to it 7.5 grammes of lactose Add the lactose litmus solution to the filtered agar and mix thoroughly Now add 1 c c of hot sterile 10 per cent caustic soda and 5 c c of freshly prepared crystal violet (0.1 gramme of crystal violet in 100 c c of distilled water) Tube off, about 10 c c per tube and sterilize for thirty minutes at 100° C on three successive days

On this medium *B. coli* colonies are pink and those of the dysentery typhoid group bluish grey and transparent

*Endo's medium (fuchsin agar)*—To 1,000 c c of distilled water in a flask add —

Powdered agar	30	gm
Leptone	10	gm
Meat extract (Lemco)	5	gm

Mix thoroughly and steam at 100° C for two hours Cool to about 60° C. and adjust the reaction to pH 7.8–8.0 Add the whipped whites of two eggs and clear in the steam sterilizer When clear, filter through thick Chardine filter paper Transfer to flasks in 100 c c amounts sterilize for half an hour on three successive days at 100° C and store in an ice chest When required, melt 100 c c of the agar mixture and add in the order given —

Chemically pure lactose	1	gm
10 per cent alcohol solution of basic fuchsin	0.5	c c
Anhydrous sodium sulphite	0.125	gm

The sodium sulphite is dissolved in a small quantity of hot sterile distilled water and is made up fresh each time

Mix thoroughly pour plates and allow to harden in the incubator before "sowing"

On this medium *B. coli* colonies are vermilion streptococcal colonies deep red, and *B. dysenteriae* and *B. typhosus* greyish

#### LEIFSON'S DESOXYCHOLATE CITRATE MEDIUM (HAYNES MODIFICATION)

For the cultivation of *Past. dysenteriae flexneri* and *Dact. dysenteriae sonnei*—Dissolve 20 gm Lab. lemco in 200 c c distilled water over a flame make just alkaline to phenolphthalein with 50 per cent NaOH boil and filter Adjust pH to 7.3 make up volume to 200 c c and add 20 gm Difco proteose peptone (Difco Lab.atories) Dissolve 90 gm agar in 3,700 c c water by one hour's steaming filter add the lemco peptone solution and mix Add 5 c c of 2 per cent neutral red and 40 gm lactose Mix thoroughly, bottle



in 100 c c amounts and sterilize by free steam (and up to 5 lbs ) for one hour  
Prepare —

SOLUTION A		SOLUTION B	
Sodium citrate	17 grm	Sodium desoxycholate	10 grm
Sodium thiosulphate	17 grm	Distilled water	100 c c
Ferric citrate	2 grm		
Distilled water	100 c c		

These solutions need not be sterilized

*For use* — Melt 100 c c of the agar base and add 5 c c each of solutions A and B in this order using separate pipettes and mixing well between. Pour plates immediately and dry the surface. Inoculate plates heavily and incubate for 24 hours. A further 24 hours incubation may be necessary. The medium is pale and slightly opaque. *B. sonnei* colonies are round about 2 mm in diameter, with a well defined edge and no appearance of roughness. They may be pale pink or become so on further incubation or storage. *B. flexneri* colonies are similar but may have a narrow plane periphery surrounding a central zone. *Paratyphosus B* colonies are larger 2-4 mm in diameter often with a black central dot. *Salmonella* colonies are similar and those of *B. typhosus* are flat and round (M Haynes 1942)

*Teague's medium* — To distilled water in a flask is added —

Agar powder	15-30 grm
Peptone	10 grm
Sodium chloride	5 grm
Meat extract (Lemco)	5 grm

Mix thoroughly and steam at 100° C for two hours. Cool add the well whipped whites of two eggs and return to steamer to clear. Filter through Whatman filter paper. Adjust the reaction to pH 7.8 then add —

Saccharose	5 grm
Lactose	5 grm

The medium is flaked off in 50 c c amounts is sterilized for half an hour on three successive days and is stored in an ice chest. When required for use it is melted and to each 50 c c is added 1 c c of 2 per cent yellowish eosin and 1 c c of 0.5 per cent methylene blue. Mix thoroughly pour plates and allow to dry off.

On this medium after eighteen hours *B. coli* colonies are deep black and opaque and *B. dysenteriae* and *B. typhosus* are colourless and transparent.

#### WILSON AND BLAIR'S MEDIUM (MODIFIED) FOR THE ISOLATION OF *B. TYPHOSUS* AND *B. PARATYPHOSUS B*

Difco dehydrated Wilson and Blair's medium powder (Difco Laboratories) 5.2 grm is suspended in 100 c c distilled water which is brought rapidly to the boil and allowed to simmer for one minute. No further sterilization is necessary. The solution is allowed to cool a little then is well mixed and poured into plates.

It is important that the medium should have a perfectly dry surface when it is used yet it should not be over dried so that a rough surface is produced. A loopful of faeces is spread evenly over half a plate and the spread area streaked over on the second half. The medium completely inhibits Gram positive cocci and nearly all strains of *B. coli*. Isolated colonies of *B. typhosus* after 24-36 hours incubation are round about 2 mm in diameter jet black.

and surrounded by a blackish zone, which has an intense metallic sheen in reflected light. Younger colonies are greenish, then develop a black centre which enlarges to fill the whole colony in a few hours. Colonies of *B. paratyphosus* resemble those of *B. typhosus* though they are a little larger after one or two days' incubation and blacken more quickly. In both instances, only well separated colonies are black, so the method of spreading should ensure that colonies are well separated. Other *Salmonella* may resemble *B. paratyphosus*, or the colonies may not blacken but remain dark green. (M. Haynes, 1912.)

#### SELECTIVE MEDIA FOR THE ISOLATION OF V. CHOLERA

*Dieudonne's blood alkali agar*—Equal parts of defibrinated ox blood and normal caustic soda solution are mixed and sterilized in a steamer at 100° C for thirty minutes on three successive days. When required for use 30 c.c. are mixed with 70 c.c. of melted nutrient agar. Plates are poured and are kept at 60° C for thirty minutes, they are left half open in the incubator overnight for the ammonia to vaporize. Organisms other than cholera and cholera like vibrios will not develop on this medium.

*Esch's medium*—500 grammes of minced lean beef are mixed with 200 c.c. of normal caustic-soda solution in a clean enamel saucepan. The mixture is simmered for two or three hours, filtered and sterilized. One part of this alkaline extract is added to two parts of nutrient agar. The transparency of this medium aids the identification of cholera colonies which are bluish grey and transparent.

*Aronson's medium*—To 100 c.c. of 3 per cent nutrient agar add 6 c.c. of a 10 per cent solution of desiccated sodium carbonate, and steam for fifteen minutes. Add 5 c.c. of a 20 per cent watery solution of saccharose 5 c.c. of a 20 per cent watery solution of dextrin 0.4 c.c. of a saturated alcoholic solution of basic fuchsin and 2 c.c. of a 10 per cent watery solution of sodium sulphite. A precipitate forms which quickly settles. Plates are poured from the supernatant fluid. Cholera colonies develop in twelve hours and show as red colonies in fifteen to twenty-four hours. *B. coli* colonies are much larger than cholera and are colourless.

#### BISMUTH SULPHITE MEDIA FOR THE ISOLATION OF V. CHOLERA (WILSON AND BLAIR MODIFIED)

*Fluid medium*—(a) To 100 c.c. boiling water add anhydrous sodium sulphite 20 gm. (b) To 10 c.c. water add bismuth ammonio citrate scales 0.1 gm. and boil. Mix (a) and (b). (c) Prepare glucose saccharose mannitol or mannose 20 gm. in 100 c.c. boiling water. (d) Cool and mix the selected sugar solution with the sulphite bismuth mixture which will have a pH of 9.4. Keep this mixture in stock. (e) Prepare 100 c.c. peptone water (peptone 1 gm., sodium chloride 2 gm. water 100 c.c., made to pH 9.1 with sodium carbonate solution—sodium carbonate 53 gm., water 400 c.c. and 1 c.c. absolute alcohol). For use add 10 c.c. of the sugar sulphite bismuth mixture to the 100 c.c. of peptone water.

*Solid medium*—(a) To 500 c.c. boiling distilled water add anhydrous sodium sulphite 100 gm. (b) To 250 c.c. boiling water add 30 gm. bismuth ammonio citrate scales. (c) Dissolve saccharose 50 gm. and mannitol 5 gm. in water 250 c.c. Mix (a) and (b) and boil for 2 minutes, cool and add (c). To this add 15 gm. sodium bicarbonate dissolved in 50 c.c. cold water. Keep as stock mixture. Prepare peptone agar (peptone 40 gm. sodium

chloride 20 grm, agar 80 grm, water 4,000 c.c., sodium carbonate solution (53 grm in 400 c.c. water) 40 c.c., autoclave and adjust without filtration to pH 8.6. For use, melt and cool to 50° C. 100 c.c. of the peptone agar, add 20 c.c. of the stock mannitol saccharose sulphite bismuth mixture, 2 c.c. of 1/1,000 phenol red and 2 c.c. absolute alcohol. Pour plates, dry and sow test material.

The medium has been found useful for the isolation of organisms of the dysentery typhoid group, for the promotion of a rich growth of true cholera vibrios, often in sharp contrast to cholera like organisms. *Coli aerogenes* organisms are suppressed and *Proteus* and *Str. faecalis* have distinctive characteristic colonies.

### STAINING METHODS

**Heidenhain's iron hæmatoxylin.**—For amœbæ, flagellates, and cysts in faecal smears

- 1 *Fixing solution* (Schaudinn's Fluid)—Absolute alcohol, one part, saturated watery solution of corrosive sublimate, two parts. Add 0.5 per cent acetic acid.
- 2 *Mordant*—4 per cent solution of iron alum in distilled water.
- 3 *Heidenhain's iron hæmatoxylin*—Hæmatoxylin 1 gramme absolute alcohol 10 c.c., distilled water 90 c.c. The hæmatoxylin is dissolved in the alcohol by heating in a large test tube over a Bunsen flame. The distilled water is similarly heated and is added to the alcoholic solution. This mixture is allowed to ripen for ten days or so, when a further 100 c.c. of distilled water are added.

*Method*—(a) Prepare thin films, thinning the faeces with normal saline if necessary, and while still wet place them surface downwards in the fixing solution (1) contained in a petri dish. Leave 15–30 minutes.

- (b) Rinse in 50 per cent alcohol, and turn films surface upwards.
- (c) Rinse several times in 70 per cent alcohol.
- (d) Wash in 70 per cent alcohol containing a few drops of Weigert's iodine and leave for fifteen to thirty minutes.
- (e) Transfer films to 70 per cent alcohol to which a crystal of sodium thiosulphate (‘hypo’) has been added. Leave till brown colour of the iodine has disappeared.
- (f) Wash in 70 per cent alcohol and pass through diluted strengths of alcohol to water.
- (g) Transfer to mordant (2) and leave six to twelve hours. Rinse rapidly in water.
- (h) Transfer to staining solution (3) and leave six to twelve hours till the films are black.
- (i) Differentiate in 1 per cent watery iron alum solution, control under microscope.
- (j) Wash in several changes of water, then in alcohols 30 per cent, 50 per cent, 90 per cent to absolute alcohol, equal parts absolute alcohol and xylol, xylol two changes, and finally mount in neutral Canada balsam.

**Phosphotungstic acid hæmatoxylin.**—For amœbæ and flagellates (Not for cysts)

Thin smears of faeces are made on cover glasses. If firm, the faeces are first emulsified with normal saline.

- (a) Half fill a Petri dish with Schaudinn's fluid, place the smears surface downwards in this solution, and leave for one hour.
- (b) Wash in water and turn films surface upwards.
- (c) Add Weigert's iodine to the water to the strength of about 1 : 10, leave fifteen minutes and wash again in water.
- (d) Transfer to water in which one crystal of hyposulphite of soda ("hypo") has been dissolved, leave till brown colour has disappeared, and wash in water.
- (e) Pour on phosphotungstic acid hæmatoxylin and leave covered on laboratory bench overnight (twelve hours). Differentiate in running water.
- (f) Wash in absolute alcohol (twice), absolute alcohol and xylol equal parts and xylol (twice). Mount in Canada balsam.

Differentiation should not be prolonged (one minute) and the films should not be left for any length of time in the alcohols. If overstained take out excess of stain very quickly with 0.5 per cent. acid alcohol and wash in water before proceeding through alcohols.

*To prepare the stain*—Hæmatoxylin 1 gramme is dissolved by heat over a Bunsen flame in 80 c.c. of distilled water contained in a large test tube. To this is added 20 c.c. of a 10 per cent. solution of phosphotungstic acid (dissolved in distilled water by heating as before). The mixture is allowed to 'ripen' for about fourteen days at room temperature before use.

Although cysts are stained well by this method for some unknown reason they burst after a day or two, and the slides are quite useless as permanent preparations.

### Heidenhain's iron-hæmatoxylin —For paraffin sections

Tissues are fixed in Zenker's fluid which is made as follows —

Potassium bichromate	2.5 grm
Sodium sulphate	1 grm
Corrosive sublimate (mercuric chloride)	5 grm
Distilled water	100 c.c.
To this stock solution is added before use acetic acid 5 c.c.	

They are fixed for several days depending on size of the tissue, are washed in running water for twelve to twenty-four hours, and are preserved in 70 per cent. alcohol. For embedding suitable portions are removed and transferred to absolute alcohol, cleared in carbon bisulphide or other clearing agent, soaked in paraffin wax with several changes till the clearing fluid is removed, and finally embedded in hard paraffin wax. Sections are cut and mounted and are treated as follows —

- (a) Remove paraffin with xylol.
- (b) Remove xylol with absolute alcohol.
- (c) Wash in 70 per cent. alcohol.
- (d) Place in 70 per cent. alcohol containing a small quantity of iodine solution to remove mercury.
- (e) Wash in water.
- (f) Leave twelve to twenty-four hours in 4 per cent. iron alum solution.
- (g) Wash in water.
- (h) Stain in Heidenhain's iron hæmatoxylin for twelve to twenty-four hours, till sections turn black.

- (i) Wash in water.
- (j) Differentiate under microscope with 1 per cent. iron-alum solution.
- (k) Wash in water.
- (l) Wash in 70 per cent. alcohol.
- (m) Rinse in two changes of absolute alcohol.
- (n) Wash in absolute alcohol and xylol, equal parts.
- (o) Wash in two changes of xylol
- (p) Mount in neutral Canada balsam.

To obtain the best results it is necessary to follow the method step by step. Sections cannot be hurried through and at no stage may they be allowed to dry.

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(See also *Shigellosis*)

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